CHAPTER 28

Frontal Variant of Alzheimer's Disease

Julene K. Johnson
Arne Brun
Elizabeth Head

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in older adults. It is accepted that AD typically begins with a progressive memory impairment and later affects language, executive function, visuospatial skills, and daily living functions (Grady et al., 1988; Hodges & Patterson, 1995; Welsh, Butters, Hughes, Mohs, & Heyman, 1991). This clinical progression is believed to reflect the relatively predictable sequence of neurofibrillary neuropathology accumulation beginning in the entorhinal cortex and spreading to the cortical regions (Arnold et al., 1991; Braak & Braak, 1991; Brun & Englund, 1981). The classic AD neuropathology also includes neuron loss, the abnormal accumulation of ß-amyloid in senile plaques with hyperphosphorylated tau proteins, and dystrophic neurites.

Atypical presentations of AD have been also described from clinical, imaging, and neuropathological perspectives. These presentations are considered "atypical" because (1) nonmemory or behavioral changes may be the first symptom, (2) nonmemory or behavioral symptoms may predominate throughout the course of the disease, or (3) the distribution of neuropathology may differ from the typical pattern. Discussion about the heterogeneity of AD began with Alois Alzheimer's first papers (1907, 1907/1987, 1911; Alzheimer, Forstl, & Levy, 1911/1991) and continues to spark debate 100 years later. The prevalence of the atypical presentations of AD is not known, but a few reports suggest that approximately 14–17% of patients with AD may have focal nonmemory presentations (Becker, Huff, Nebes, Holland, & Boller, 1988; Galton, Patterson, Xuereb, & Hodges, 2000).

One could argue that it is important to define both the "typical" and "atypical" presentations of a disease. However, one could also argue that it is not scientifically useful to focus on variations in a clinical or neuropathological presentation that represent one disease, and that these variations do not have an underlying biological basis. Several authors have hypothesized the existence of subgroups in AD (Cummings, 2000; Vogt, Vogt, & Hof, 2001). Because the definitive diagnosis of AD can only be determined at autopsy, an accurate clinical diagnosis of AD remains critical. Until we have a definitive clinical diagnostic test for AD, we are left with improving our clinical tools. As disease-specific therapeutics become available, it will be even more important to diagnose AD accurately.

Our goal in this chapter is to discuss the heterogeneity of AD, with a particular emphasis on the frontal variant of AD. We argue that studying atypical presentations of AD can be useful for understanding brain–behavior relationships and the underlying biological mechanisms of AD.

EARLY OBSERVATIONS OF HETEROGENEITY IN AD

In the early 1900s, Alois Alzheimer (1906, 1907, 1911) described the clinical and neuropathological findings of two patients who presented with an unusual progressive disorder in later middle life. The first patient, a 51-year-old woman referred to as Auguste D, suddenly developed jealousy toward her husband and shortly thereafter experienced a rapid decline in memory, frequently got lost, and had delusions that people were going to kill her. As described in Perusini (1909, 1909/1987), Alzheimer examined Auguste D and described severe deficits in language, orientation, and memory, as well as delusions and anxiety. He considered the deficits in language to be focal, which contrasted with a relative preservation of motor skills. Alzheimer noted:

> During the course of the disease symptoms appeared which could be considered focal symptoms; sometimes these were prominent and sometimes quite faint. But they were always mild. Mental regression advanced quite steadily. After four and one half years of illness the patient died. (1907/1987, p. 2; original German in Note 1)

He considered the clinical presentation atypical because it did not resemble other, known clinical patterns with an onset in later middle age. At autopsy, Alzheimer found an "evenly affected atrophic brain without macroscopic foci" and the deposition of cored plaques and intracellular fibrils (now known as neurofibrillary tangles). A few years later, Alzheimer (1911) described a second patient, Johann F, a 56-year-old man who first became "quiet and dull," and then 1.5 years later developed symptoms of forgetfulness, getting lost, overeating, poor hygiene, and difficulty performing simple tasks. Alzheimer again considered the presence of focal symptoms (i.e., agnosia, aphasia, apraxia), noting, however, that they were difficult to analyze because of severe language deficits. At autopsy, he discussed the distribution of neuropathology:

> A further peculiarity of the present case was the localization of the alterations. Even if we were dealing with a diffuse disease of the cortex alone, the parietal and temporal lobes bilaterally were unmistakably especially affected and much more so than the frontal brain. In ordinary cases of senile dementia, the frontal brain is the most severely diseased, as has been found only recently by Simchowicz. (1911/1991, p. 92; original German in Note 2)

It is remarkable that Alzheimer noticed a predominance of atrophy in the parietal and temporal lobes, while noting that others, namely Simchowicz (1910), had recently observed prominent atrophy in the frontal cortex. Although he described evenly distributed gross atrophy of Auguste D's brain, Alzheimer observed focal parietal and temporal lobe atrophy in the brain of Johann F. Other early researchers, such as Fischer (1907/1987), Bonfiglio (1908/1987), and Perusini (1909), focused on describing the specific histopathological findings and not the regional distribution of neuropathology. It is clear that Alzheimer thought about both focal symptoms and focal atrophy patterns. His prior interest in dementia in older adults and "general paralysis" (i.e., neurosyphilis) (Alzheimer, 1898, 1899, 1899/1991) provided a good background for differentiating between AD and other mental disorders in elderly individuals.

From these early descriptions through the 1950s, however, AD was known as a global disorder that was secondary to diffuse neuropathological involvement. A disproportionate emphasis was placed on differentiating presenile and senile dementia based on the age of onset (Benson, 1986; Katzman & Bick, 2000). The issue of clinical and pathological heterogeneity was discussed, however, to a lesser degree. A common theme involved differentiating between AD and Pick's disease. For example, Rothschild and Kasanin (1936) described a 49-year-old man who developed changes in behavior (i.e., childish, euphoric, overactive) and cognition that resembled that in Pick's disease. At autopsy, the patient had focal atrophy of the frontal cortex, widespread cell loss and plaques, and tangles characteristic of AD. Delay and Brion (1962) identified three groups with focal atrophy, including one group with focal frontal cortex atrophy. Others also described focal frontal lobe atrophy in patients with AD neuropathology (Abeley, Desclaux, Naudascher, & Suttel, 1945; Divry, Levy, & Titeca, 1935; Kreindler, Hornet, & Appel, 1959; Liebers, 1939; Moyano, 1932; Seitelberger & Jellinger, 1958; Tariska, 1970). Berlin (1949) described a patient who had focal

temporal lobe atrophy, a combination of plaques and tangles, but also "inflated cells of Pick." Observations of focal (circumscribed) cerebral atrophy on gross examination of the brain and a combination of both AD and Pick's disease neuropathology in some cases led early clinicians to question whether AD and Pick's disease could be differentiated clinically (Chlopicki & Rzewuska-Szatowska, 1971; Sjogren, Sjogren, & Lindgren, 1952).

In 1957, Lars Gustafson and David Ingvar at the University of Lund (Sweden) began a clinical and metabolic brain imaging study, with the goal of prospectively following the development of symptoms and imaging changes in dementia and ultimately improving diagnostics and therapy (Gustafson, Hagberg, Holley, Risberg, & Ingvar, 1970; Ingvar et al., 1968). This study also allowed for the study of atypical presentations of dementia. The first neuropathological findings from this study were presented at the Seventh International Congress of Neuropathology in Budapest in 1974 (Brun, Gustafson, & Ingvar, 1975), where the authors reported a relationship between neuropathological findings, neuropsychiatric symptoms, and regional cerebral blood flow in presenile dementia. Additional studies addressed the relationship between neuropathology and clinical symptoms. Based on a histological grading of the regional severity of the neuronal degeneration, the team found a predominance of degeneration in the limbic system (i.e., amygdala, hippocampus) and inferior temporal-parietal areas (Gustafson, Brun, & Ingvar, 1977). In addition, a focus on the posterior cingulate cortex was added (Brun & Gustafson, 1976, 1978). This neuropathological pattern was later confirmed by PET imaging (Minoshima, Foster, & Kuhl, 1994; Minoshima et al., 1997), and the regional pattern of pathology was further systematized by Braak and Braak (1991, 1995). In 1970, Lauter discussed the difference between senile and presenile AD, pointing out that senile dementia was more global than presenile dementia, with less pronounced temporoparietal focus and relatively more frontal involvement in the senile form.

Much of the early work on heterogeneity focused on defining the clinical syndromes of AD and Pick's disease. The early researchers also were interested in determining whether AD was a focal or global disorder. These early studies highlight the consideration of both typical and atypical presentations of AD.

CLINICAL HETEROGENEITY OF AD

After almost 100 years since Alzheimer described his first cases of AD, the issue of clinical heterogeneity still stimulates discussion. In addition to the traditional clinical and neuropathological approaches, new data from neuroimaging and behavioral studies have added to the understanding of AD heterogeneity. A renewed interest in focal presentations of dementia emerged in the 1980s, when several authors hypothesized that AD might underlie a number of focal presentations of dementia (Chui, Teng, Henderson, & Moy, 1985; Kirshner, Webb, Kelly, & Wells, 1984; Mayeux, Stern, & Spanton, 1985). However, only a few were autopsy-confirmed, including patients with AD and pronounced behavioral symptoms (Brun, 1987; Tariska, 1970) or disproportionate impairment on visuospatial (Crystal, Horoupian, Katzman, & Jotkowitz, 1982; Faden & Townsend, 1976; Hof, Bouras, Constantinidis, & Morrison, 1989) or language domains (Pogacar & Williams, 1984). These initial clinicopathological studies also made the point that focal clinical symptoms could be associated with focal and disproportionate neuropathology in corresponding brain regions. For example, patients with pronounced behavioral symptoms were found to have pronounced AD neuropathology in the frontal cortex. Based on the observations of cognitive heterogeneity, several authors proposed the existence of distinct subgroups in AD (Becker et al., 1988; Martin et al., 1986; Mayeux et al., 1985), a concept that has persisted (Black, 1996; Cummings, 2000; Galton et al., 2000; Martin, 1990; Vogt et al., 1999, 2001). In 1987, the National Institutes of Health sponsored a conference that focused on the heterogeneity of AD (Friedland et al., 1988), and an open peer commentary involving several authors was published in 2000 (Cummings, 2000). In a large study of 407 autopsy-confirmed patients with AD, Kanne, Balota, Storandt, McKeel, and Morris (1998) correlated three subgroups with different distributions of neuropathology, including frontal cortex/mental control, temporal cortex/verbal memory, and parietal cortex/visuospatial subgroups.

Clinical heterogeneity of AD has also been studied from a neuroimaging perspective. Metabolic imaging studies suggest a relationship between focal cognitive deficits and metabolic changes in specific brain regions. In one of the first detailed early studies of cognitive and neuroimaging heterogeneity in AD, Foster and colleagues (1983), using positron emission tomography (PET), found that patients with AD who had prominent visuospatial impairment had focal hypometabolism in the right parietal cortex, whereas focal language deficits were associated with marked hypometabolism in the left hemisphere. Martin and colleagues (1986) used factor analysis of cognitive scores and identified patients with probable AD who had prominent language or visuospatial deficits. When correlated with PET, patients with prominent language deficits had greater left temporoparietal hypometabolism, whereas the patients with prominent visuospatial deficits had greater right temporoparietal hypoperfusion. Others confirmed that patients with AD and prominent visuospatial deficits have lower blood flow in the parietal cortex, whereas patients with prominent language deficits have pronounced hypometabolism in the left perisylvian region (Bokde et al., 2001; Celsis, Agniel, Rascol, & Marc-Vergnes, 1987; Chase et al., 1984; Grady et al., 1990; Haxby, Duara, Grady, Cutler, & Rapoport, 1985; Haxby et al., 1988; Mann, Mohr, Gearing, & Chase, 1992; Pietrini et al., 1996). Grady and colleagues (1990) found a subgroup of patients with a combination of temporoparietal and frontal cortex hypometabolism in patients with AD and behavioral disturbances, and Waldemar and colleagues (1994) found frontal hypometabolism in 19 of 25 patients with AD.

Although episodic memory dysfunction is still considered the most prominent cognitive symptom in AD (Lange et al., 2002; Welsh et al., 1991), it is now more widely recognized that AD can present with disproportionate impairment in nonmemory domains, such as executive functioning, visuospatial, and language abilities. However, the National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984) require the presence of a memory deficit as one of the affected cognitive domains for a clinical diagnosis of probable or possible AD. The clinical diagnosis of dementia, as outlined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994), also requires the presence of a memory deficit that is sufficient to produce a functional impairment. These criteria may therefore exclude some atypical presentations of AD (Mayeux et al., 1985) and create a diagnostic challenge for atypical presentations of AD.

EXECUTIVE FUNCTION IN AD

"Executive function" is cognitive ability that involves the planning and execution of complex, goal-oriented behaviors (Lezak, 1995; Stuss & Knight, 2002). More specifically, executive function includes attentional control, setting of goals, set shifting, abstraction, response monitoring, and flexibility. Executive function can be subdivided into subcomponents based on functional and anatomical bases; however, there is not yet agreement on the best models of executive function. Executive dysfunction is a central feature of several neurodegenerative and psychiatric disorders, such as frontotemporal dementia (FTD), progressive supranuclear palsy, schizophrenia, and major depression. In the early stages of AD, some patients report difficulties with concentration, multitasking, problem solving, and, sometimes, behavior. However, executive dysfunction is traditionally not considered to be a core feature of AD (Nebes & Brady, 1989). Several studies suggest that executive dysfunction occurs later in the course of AD (Nestor, Parasuraman, Haxby, & Grady, 1991; Pillon, Dubois, Lhermitte, & Agid, 1986).

More recent studies suggest that executive dysfunction may be an early feature of AD (Binetti et al., 1996; Collette, Van der Linden, & Salmon, 1999; Cummings & Benson, 1992; Sgaramella et al., 2001). In one of the early longitudinal imaging studies, Grady and colleagues (1988) studied memory, executive function, and language in patients with early AD. The results suggested that executive dysfunction (i.e., Porteus Maze Test, Trail Making Test B, Raven's Progressive Matrices) occurred after memory impairment but before visuospatial and language impairment. Other studies have attempted to identify which subcomponents of executive function are impaired versus pre-

served in AD (Duke & Kaszniak, 2000; Perry & Hodges, 1999). In another early study, Laflèche and Albert (1995) found that 20 patients with Ad and mild dementia performed significantly worse than controls on measures of executive function that required concurrent manipulation of information (i.e., Trail Making Test B, Self-Ordering Test, verbal fluency [FAS], Hukok Test). Other studies suggest that sustained and divided attention remains intact in early AD, whereas selective attention is impaired (Laflèche & Albert, 1995; Nebes & Brady, 1989; Perry, Watson, & Hodges, 2000). Inhibitory function in early AD is also impaired (Collette, Van der Linden, Delrue, & Salmon, 2002). Perry and colleagues (2000) also argue that selective attention is affected only after an initial amnestic stage in early AD. However, when comparing AD with other frontal lobe dementias, most studies suggest that patients with FTD exhibit greater executive dysfunction than those withAD (Pachana, Boone, Miller, Cummings, & Berman, 1996; Perry & Hodges, 2000; Razani, Boone, Miller, Lee, & Sherman, 2001).

Evidence also suggests that there is a subgroup of AD patients with disproportionate executive impairment and behavioral disturbances. We have discussed early neuropathological studies and further discussion about a frontal variant of AD from a clinical and neuropathological perspective follows. Binetti and colleagues (1996) split patients with mild AD into two groups based on executive function measures: those who scored below one standard deviation of controls on tests of executive function (i.e., Wisconsin Card Sorting Test [WCST], release from proactive interference, verbal fluency, and Stroop) and those who scored within the normal range. The patients with and without executive impairment performed similarly on tests from other cognitive domains (i.e., memory, language, visuospatial), suggesting that a subgroup of patients with disproportionate executive impairment. Others have observed a prominent executive dysfunction with relatively preserved memory in AD (Baddeley, Della Sala, & Spinnler, 1991; Becker, 1988; Becker, Bajulaiye, & Smith, 1992). Below we discuss the clinical and pathological characteristics of a frontal variant of AD.

Thus, executive dysfunction appears to be an important cognitive domain in the understanding of AD. The underlying etiology of executive dysfunction in AD is also not yet known. Cummings (1998) suggests that a disruption in the frontal–subcortical circuits may contribute to executive dysfunction in AD.

BEHAVIORAL CORRELATES OF EXECUTIVE DYSFUNCTION IN AD

Executive dysfunction in AD has also been linked with behavioral symptoms (e.g., apathy, aggression, depression, and psychosis) and functional impairment. Additional studies using brain imaging have found an association between behavioral disturbances and frontal lobe dysfunction. A few studies have explored the relationship with specific behavioral syndromes, neuropathology, and genetics.

Apathy in AD has been associated with executive dysfunction, functional impairment, and prefrontal hypometabolism. Several studies suggest that patients with AD and apathy perform worse on tests of executive function than patients with AD without apathy (Kuzis, Sabe, Tiberti, Dorrego, & Starkstein, 1999; McPherson, Fairbanks, Tiken, Cummings, & Back-Madruga, 2002). Patients with AD with apathy and prominent executive dysfunction also have more functional impairment on activities of daily living (Boyle et al., 2003; Stout, Wyman, Johnson, Peavy, & Salmon, 2003). A pronounced hypometabolism in prefrontal and anterior temporal cortex in patients with AD and significant apathy (Craig et al., 1996) suggests that frontal lobe dysfunction may be related to the development of apathy.

Executive dysfunction has also been linked with agitation and aggression. For example, Chen, Sultzer, Hinkin, Mahler, and Cummings (1998) found that poor performance on tests of executive function was associated with agitation, disinhibition, and functional impairment. Another study found that patients with AD and poor executive function had more agitation and functional impairment than patients with AD and intact executive function (Back-Madruga et al., 2002; Cummings & Back, 1998). Aggression in AD patients correlates with left frontotemporal hypometabolism (Hirono, Mega, Dinov, Mishkin, & Cummings, 2000; Sultzer et al., 1995) and is associated with an increase in neurofibrillary tangles

in the orbitofrontal and anterior cingulate cortex (Tekin et al., 2001). Agitation in AD has been linked to polymorphisms associated with serotonin (Assal et al., 2004; Craig, Hart, Carson, McIlroy, & Passmore, 2004; Sukonick et al., 2001) and the apolipoprotein ε4 allele (Craig, Hart, McCool, McIlroy, & Passmore, 2004).

Finally, psychosis in AD has also been linked with executive dysfunction and frontal hypometabolism. For example, Swanberg, Tractenberg, Mohs, Thal, and Cummings (2004) found a relationship between poor performance on tests of executive function, psychosis, and greater impairment on activities of daily living. Psychosis in AD has also been linked to prefrontal hypometabolism (Mega et al., 2000; Sultzer et al., 1995, 2003). Early studies suggested an increase in frontal cortex neuropathology in patients with AD and psychosis (Zubenko et al., 1991); however, better controlled studies have not found this pattern (Forstl, Burns, Levy, & Cairns, 1994; Sweet et al., 2000). Psychosis in AD is also associated with serotonin polymorphisms (Holmes, Arranz, Powell, Collier, & Lovestone, 1998; Nacmias et al., 2001) and an interleukin promoter polymorphism (Craig, Hart, et al., 2004).

There is clearly an link between executive function, behavior, and functional impairment in AD. The underlying reason for this link is not yet known. However, genetic and neuropathological studies may improve understanding. It appears that patients with AD and prominent executive dysfunction are at risk for poor clinical outcomes.

FRONTAL VARIANT OF AD

As can be gleaned from a review of the history of AD, there has been a long-standing interest in examining the heterogeneity of AD. Over the years, it became clear that the typical presentation of AD involves an early decline in memory, followed by deficits in other domains and a typical predominance of plaques and tangles in the hippocampal formation and temporoparietal cortex. However, as described earlier, there were early reports of patients with prominent frontal atrophy (on gross examination), AD neuropathology, and sometimes a significant behavioral syndrome.

However, it was not until the work by Brun and Gustafson that the clinicopathological relationship between behavioral dysfunction and a predominance of frontal cortex neuropathology was better linked. Brun (1987) and Gustafson (1987) described the neuropathological findings on 26 patients with a frontal or frontotemporal presentation of dementia. Of these, 16 (62%) had neuropathological evidence of neuron loss, gliosis, and spongiosis in the superficial layers, primarily in the frontal and, to a lesser extent, temporal lobes, currently referred to as dementia lacking distinctive histopathological features (DLDH) or frontotemporal lobar degeneration (FTLD). The insula and cingulate gyrus were also affected. The remaining patients had Pick's disease (n = 4), Creutzfeldt–Jakob disease (n = 3), AD (n = 2), and one patient had thalamic infarctions. Appendix 28.1 includes the clinical summaries for the two patients with AD. Both patients had early and prominent changes in personality, judgment, and memory, and focal frontal hypometabolism on imaging. At autopsy, Brun described a predominance of plaques and tangles, neuronal loss, gliosis, and spongiosis in the frontal cortex when compared with other cortical regions. In these two patients, the topographic pattern for the severity of the AD departed markedly from the predominant temporoparietal pattern, with a far more pronounced degeneration in the prefrontal area than usual. An incomplete white matter infarction could be added, though it was not exclusively frontal. In the second case, there was evidence of a diseased striatum. This may explain the impression of a frontal dysfunction that was possibly reinforced by the frontal blood flow decrement. Thus, these two cases suggest a strong association between the clinical profile, brain imaging, and a predominance of AD neuropathology in the frontal cortex. They also showed that AD can be associated with a FTD-like phenotype.

Later in 1999, Johnson, Head, Kim, Starr, and Cotman were studying an atypical presentation of AD that involved early and prominent impairments on tests of verbal fluency and set shifting. We hypothesized that patients with AD and prominent executive dysfunction in the early stages of dementia would also have a predominance of pathology in the prefrontal cortex. After reviewing pathology-confirmed AD cases with clinical data from the mild stage of AD (i.e., Mini-Mental State Exam [MMSE] ≥ 18), we identified three patients with an impairment on two tests of executive function

(i.e., verbal fluency [FAS] and the Trail Making Test). We then compared these patients with three typical patients with AD matched in dementia severity, age, education, and extent of neurofibrillary tangle pathology in the entorhinal cortex (to control for disease severity). The groups did not differ on measures of memory, language, or visuospatial skills. However, the frontal variant AD group had an approximately 10 times greater degree of neurofibrillary tangle pathology in the prefrontal cortex (area 8). We suggested that the correlation between cognitive patterns and neuropathological distribution represented a subgroup of AD with prominent executive dysfunction and greater-than-expected prefrontal cortex neuropathology.

Vogt and colleagues (1999) described an 85-year-old man (FG) who exhibited significant behavioral changes (i.e., paranoia, aggression) and executive dysfunction, and AD neuropathology at autopsy. His first symptom was a severe paranoia related to truck drivers. The plaques and tangles were most prominent in the prefrontal cortex and cingulate. In another study, Johnson, Vogt, Kim, Cotman, and Head (2004) described a nondemented individual with an isolated impairment on a test of executive function and preserved memory, with a predominance of both tangle and plaque neuropathology in the prefrontal cortex when compared to other regions.

There also may exist a relationship with genetics and neurobiology. Several authors have found a presenilin-1 mutation associated with a familial FTD phenotype (Raux et al., 2000; Tang-Wai et al., 2002), including one autopsy-confirmed patient with Pick's disease (Dermaut et al., 2004). Another recent study found a presenilin-1 polymorphism in an autopsy-confirmed patient with AD with an FTD phenotype (Goldman et al., 2005). In terms of underlying biological differences, Talbot and colleagues (2000) found a significant decrease in a marker of membrane function, phospholipase A2, in the frontal cortex when compared with other brain regions and typical patients with AD.

Although there are a number of reports about patients with a frontal or executive presentation of AD, the phenotype is not yet thoroughly described. A combination of cognitive, behavioral, functional, brain imaging, genetic, and neuropathological studies have not yet been done.

FRONTAL CORTEX NEUROPATHOLOGY IN AGING AND AD

To better understand why the frontal cortex is more affected in some patients with AD, we review the literature about the frontal cortex in healthy aging and AD. The aging brain suffers a general atrophy that is, however, most marked in the white matter and cortex of the frontal lobe, second only to the hippocampus. Frontal white matter may be particularly vulnerable to the aging process as described in studies using *in vivo* imaging procedures, as well as postmortem autopsy experiments (Buckner, 2004). With age, frontal cortical atrophy (Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998), a loss of white matter integrity (Madden et al., 2004; O'Sullivan et al., 2001), and white matter lesions detected as hyperintensities (de Groot et al., 2000) are all associated with poorer cognition and, specifically, executive function in nondemented older adults. The mechanisms underlying cortical atrophy and white matter loss/dysfunction have not been fully elucidated but may be related to observations in postmortem studies. For example, genes important for maintaining synaptic plasticity, vesicular transport, and mitochondrial function are downregulated in the aged frontal cortex (Lu, 2004). Some studies of protein levels reflecting synapse loss are consistent with gene expression studies and demonstrate synapse protein loss (Liu, Erickson, & Brun, 1996; Masliah, Mallory, Hanson, DeTeresa, & Terry, 1993), but others show no change with age (Haas, Hung, & Selkoe, 1991; Honer, Dickson, Gleeson, & Davies, 1992). A study using unbiased, stereology-based estimates of synapse number in the frontal cortex also suggested that the frontal cortex synapse number appears unaffected with age in nondemented individuals (Scheff, Price, & Sparks, 2001). Variable reports may stem from the cases included in the study, the region of frontal cortex examined, and other possible methodological issues (e.g., types of synapse number and quantification methods). Liu and Brun (1995), on the other hand, found a progressive, age-related loss of frontal cortical synapse density amounting to roughly 40% between ages 20 and 100. Mitochondrial dysfunction observed in the frontal cortex of older adults (Ojaimi, Masters, Opeskin, McKelvie, & Byrne, 1999) and cumulative oxidative damage observed with age (Ames & Shigenaga, 1992) may also be related

to neuron dysfunction or losses, and/or cortical atrophy reported in imaging studies, and is consistent with decreased gene expression results. Another sign of frontal pathology is increased astrogliosis (Unger, 1998), and messenger RNA (mRNA) levels for the astrocyte cytoskeletal protein glial fibrillary acidic protein, also increase with age (Nichols, Day, Laping, Johnson, & Finch, 1993). In combination, these results suggest that the frontal cortex is vulnerable to aging, and neurobiological changes may be reflected in impairments in frontal lobe function. Last, from a phylogenetic and ontogenetic point of view, the frontal lobes, with their protracted and late maturation, would be expected to be selectively vulnerable, which is all the more obvious when compared with the adjoining sensorimotor cortex that is old, early, and robust.

In AD, significant frontal cortex pathology is observed, but it is not typically a focus of neuropathology studies. AD is characterized by widespread senile plaque and neurofibrillary tangle (NFT) formation throughout association cortex and within limbic regions, leaving primary sensory or motor cortex relatively intact (Brun & Gustafson, 1976). In 1991, a careful description of a large number of samples in an autopsy study by Braak and Braak led to the description of various stages of either senile plaque or NFT distribution. In this study, cases that had come to autopsy from several hospitals, but not from geriatric psychiatry institutions, were used. Of 83 cases, 29 had a clinical diagnosis of dementia, but 8 subsequently did not have AD pathology, and 4 cases were adults with Down's syndrome; the remaining cases were clinically undescribed. Six stages of NFT formation were observed with the entorhinal cortex and hippocampus affected early in the disease. Although, later in the disease, neocortex accumulates NFT pathology, Braak and Braak staging does not differentiate between frontal cortex and other regions of the brain as being more or less affected. With senile plaque accumulation, only three stages could be consistently categorized due to significant interindividual variability. Stage A was characterized as showing β-amyloid (Aβ) within the basal forebrain (including basal portions of the frontal, temporal and occipital lobes) including weakly stained clouds of Aß within the presubiculum and entorhinal cortex.

In a more recent study, a series of 51 prospectively followed, clinically characterized patients with autopsies were used to describe four phases of Aß deposition. In this study, Aß appears in neocortex (frontal, parietal, temporal, and occipital) early in disease, followed by entorhinal, hippocampus, amygdala, and insular cortex (Thal, Rub, Orantes, & Braak, 2002).

Thus, based on careful descriptions of large autopsy series, the frontal cortex appears to be affected significantly by Aß, possibly early in AD, but late in disease by NFT accumulation. This contrasts with the hippocampus and underlying cortex, where NFT formation predominates early in disease. Selective memory deficits in mild cognitive impairment (MCI) and more severe memory deficits in AD may be related to early involvement of limbic structures but also possibly to frontal cortex dysfunction. A recent stereology-based study of NFT and neuron counts that included a subregion of the frontal cortex (area 9) demonstrated a significant association between overall dementia severity, measured by MMSE, and frontal cortex pathology, in addition to hippocampal and entorhinal cortex pathology (Sarazin et al., 2003). However, a subset of patients with AD presents with early and predominant executive dysfunction, as described below.

In addition to senile plaques and NFT, white matter pathology also reflects neuronal dysfunction. Frontal cortex infarcts but, in particular, incomplete white matter infarcts (i.e., not associated with complete infarcts) may cause or reinforce a frontal dysfunction. They may be part of more general white matter damage, but the frontal white matter is a common preferential location in AD (Brun & Englund, 1986). Most likely, this preferential frontal white matter damage is caused by repeated episodes of hypoperfusion due to blood pressure drops, in addition to arteriolosclerosis that affects the autoregulatory vascular response. This may develop in discrete steps and may build up in a seemingly progressive course. Incomplete white matter infarcts also surround lacunes in Binswanger's disease when they may engage wide areas, particularly the frontal white substance. The mechanism by which they may cause dysfunction is by partial undermining of the cortex or destroying cholinergic transport routes passing through the white matter on their way from nucleus basalis of Meynert via the extreme capsule to the frontal cortex. This way they may thus add or reinforce a frontal

dysfunction in AD and other dementias. In the case of transport blockage, they may explain a beneficiary effect of cholinergic treatment in vascular diseases.

In addition, selective pyramidal neuron loss (Hof, Bouras, Constantinides, & Morrison, 1990), loss of synaptic proteins (Masliah et al., 2001) or reduced expression of genes related to synaptic vesicle trafficking (Yao et al., 2003), loss of synuclein immunoreactivity, and myelin basic protein immunoreactivity (Wang et al., 2004a, 2004b) have all been detected in frontal cortex. Synapse loss in the frontal cortex may be an early event in AD progression, because a 25% loss of synaptophysin has been reported in patients with a Clinical Dementia Rating (CDR) of 0.5 (Masliah et al., 2001). Furthermore, loss of synuclein and myelin basic protein in frontal cortex correlates with deficits in frontal function (Wang et al., 2004a, 2004b). Myelin basic protein loss may be a mechanism underlying reports of significant white matter pathology in AD visualized by *in vivo* imaging.

Establishing the neurobiological mechanisms underlying impaired frontal cortex function in AD is challenging. First, postmortem studies are more heavily weighted toward the examination of end-stage disease cases, which is an unavoidable limitation to studying AD. Less frequent are the number of studies of individuals that came to autopsy earlier in the disease process, when selective cognitive deficits may be apparent. These cases can be invaluable for establishing a link between cognition and neuropathology, but they are infrequent. In a cohort of 210 subjects with possible AD, only nine subjects exhibited atypical signs of prominent frontal dysfunction (Villareal et al., 2003). But these atypical cases can be instructive (Vogt et al., 2001). For example, autopsy studies in nondemented individuals with select and severe impairment in memory (amnestic MCI) provided solid evidence that this is an early form of AD based on significant pathology in the hippocampus and entorhinal cortex (Morris et al., 2001). Focal frontal atrophy was also observed in another case study of a patient with early signs of dysexecutive syndrome and was also linked to diffuse frontal Aß deposition (Vogt et al., 1999). We recently reported a case study of an individual with a selective and severe impairment in executive function that, at autopsy, exhibited significant frontal senile plaque and NFT pathology (Johnson et al., 2004). Second, there may be a bias toward selectively studying the hippocampus given that AD is commonly associated with memory impairment. Although frontal cortex specimens may be included in these studies, they are less likely to be a focus of the link between cognition and neuropathology in AD. This may, in turn, be due to inherent difficulties with studying the neuropathology of the frontal cortex. The frontal cortex is complex and contains multiple anatomical and functional domains, and selection of key regions of interest is difficult to establish. Based on models of how AD pathology begins and spreads (Braak & Braak, 1991, 1995), it is surprising that executive dysfunction would occur early in AD, because the frontal cortex is affected later in the course.

CURRENT CONCEPTUALIZATION OF FRONTAL VARIANT OF AD

The key question remains: Does the clinical heterogeneity in AD reflect biologically distinct disorders or variability in the expression of the same disease? It is still not possible to answer this research question definitively. However, 100 years of research about AD has helped to focus the question. There is now more clinical, cognitive, imaging, behavioral, genetic, and neuropathological evidence to suggest that AD is heterogeneous and subgroups are likely. However, the underlying neurobiological basis of the heterogeneity in AD remains a mystery.

Several authors have hypothesized that heterogeneity in AD is highly influenced by the location, degree, and type of neuropathology. Clearly, the pattern of neurodegeneration in AD is not uniform (Brun & Englund, 1981; Vogt et al., 2001), and there is considerable evidence regarding the selective vulnerability of different cortical regions and subregions (Detoledo-Morrell et al., 1997; Morrison & Hof, 2002; Vogt et al., 1999). There is also evidence that cognitive and behavioral deficits vary according to which brain areas are most involved (Kanne et al., 1998). It is not yet known whether there is variability in the location of initial AD neuropathology. The type of AD neuropathology may also affect heterogeneity. Whereas tangles only are increased in some reports of focal presentations of AD, others report an increase in both plaques and tangles. Other neuropathological lesions, such as white matter loss or vascular changes, may also influence the heterogeneity. However, there are

not good methods to evaluate the interaction among all these pathological variables. It is also possible that multiple etiologies or comorbid medical conditions could affect the heterogeneous presentation of AD. For example, coexistent Lewy body, cerebrovascular, white matter pathologies can affect the clinical expression of AD (Lopez et al., 2000). It is also plausible that focal deficits are influenced by multiple brain regions. For example, executive dysfunction can arise from both prefrontal cortex or subcortical damage, thus damaging frontal–subcortical circuits or other areas connected with the prefrontal cortex (Collette et al., 2002; Cummings, 1998; Perry & Hodges, 1999).

There are also hints that genetics may influence the heterogeneity in AD. The strongest support for this hypothesis comes from studying in association of genetic polymorphisms and specific behavioral syndromes in AD. Another hypothesis is that developmental or premorbid vulnerabilities may interact with environmental factors to create heterogeneity of disease expression.

It is also important to keep in mind that clinical heterogeneity could reflect diagnostic inaccuracy. In fact, many of the studies we have discussed do not have pathological confirmation of AD. Although diagnostic accuracy at tertiary centers for typical AD is good (> 90% accurate) (Lopez et al., 2000), diagnosis of atypical AD remains difficult. Focal presentations of dementia can be caused by a number of neurodegenerative diseases (Black, 1996; Kramer & Miller, 2000). It is important to study heterogeneity in the preclinical or early stages of dementia.

Thus, the frontal subgroup or variant of AD remains a hypothesis. New clinical, imaging, and genetic approaches to the heterogeneity of AD will improve diagnosis and allow better differentiation from non-AD dementias. Studying the early stages of dementia, such as the frontal presentation of MCI, will also help elucidate the neurobiological basis. The probability of a frontal presentation of AD also expands the need for better differential diagnosis and better comparisons with other neurodegenerative diseases that affect the frontal lobes (e.g., frontotemporal dementia, Huntington's disease, Creutzfeldt–Jakob disease). Future research should combine clinical, cognitive, behavioral, brain imaging, genetics, and neuropathological approaches to studying heterogeneity in AD.

APPENDIX 28.1. CLINICAL DESCRIPTIONS OF CASES 1 AND 2 OF BRUN (1987)

Case 1. An 81-year-old woman (EL) previously in good health started around age 65 to suffer from personality changes with poor judgment, increasing forgetfulness, restlessness, unrest, and general loss of interest. At age 73, she was admitted under the diagnosis of senile dementia. Somatically, her condition was unremarkable. She became increasingly confused and disturbed, aggressive, and talked incoherently. She was disoriented as to time, person, and whereabouts, and could not carry on a conversation. She was unable to manage her daily living activities. She soon became incontinent and bedridden, lying in her bed in a fetal position, now with increased general muscle tone and with a left-sided positive Babinski. She also developed epilepsy, that began with a couple of grand mal seizures and a diffusely coarse, dysrythmic electroencephalogram (EEG) with a left-sided focus, though later her epilepsy subsided and became less disturbing to the patient and her surroundings. Regional cerebral blood flow recorded 6 years after admission showed bilateral prefrontal hypoperfusion, with a slight left–right asymmetry; 3 years later, it showed marked left-sided frontal and frontotemporal hypoperfusion, yet a year later indicated 20% reduction in left-hemispheric average flow and marked focal decrement frontally and frontotemporally on both sides. The clinical picture was considered somewhat unclear but suggestive of FTD. Her dementia progressed and she died at the age of 81. Autopsy showed pulmonary emboli and bilateral bronchopneumonia as the cause of death. Grossly, the brain weighed 960 grams and showed a general atrophy that was most marked in the frontal lobes. Microscopic examination revealed AD, and in accord with the gross atrophy pattern, the AD changes were most intense in the prefrontal areas. There were no complete infarcts, but there were incomplete infarcts, though more parietally than frontally. The motor cortex was well preserved, as was the calcarine cortex, and the parietal cortex took an intermediate position with regard to severity of microscopic AD changes.

Case 2. A woman (BH), age 70 at death, was admitted at age 68 under a suspicion of FTD. Previously healthy, she suffered from memory difficulties from age 65 on. On admission she had urinary incontinence and ate only on command. Her condition rapidly worsened and she became confused and had to be cared for around the clock. Two years after admission, she was completely

disoriented but could state her name and answer questions only with a yes. Regional cerebral blood flow studies indicated a frontal dysfunction. She was unconcerned, disoriented, and denied any somatic or psychiatric symptoms. Three years after admission, she was apraxic, with a somewhat staggering, short-paced gait. Computed tomography (CT) showed a general brain atrophy, and a repeat cerebral blood flow study indicated a frontal hypoperfusion; now, in addition, there was a postcentral flow decrement with some side asymmetry. Postmortem, only the brain was available for analysis. It weighed 910 grams, with a general atrophy, though somewhat more pronounced basotemporally. Microscopy revealed AD with an unusually severe involvement of the frontal lobes, including the anterior portion of the cingulate gyrus. Also, somewhat unusually, there was a degeneration of the caudate nucleus with gliosis, though with only scattered plaques. There were also cavitating infarcts underneath the sensorimotor gyri, and a general white matter incomplete infarction that included the frontal lobes.

NOTES

1. "Im weiteren Verlaufe treten die als Herdsymptome zu deutenden Erscheinungen bald stärker, bald schwächer hervor. Immer sind sie nur leicht. Dagegen macht die allgemeine Verblödung Fortschritte. Nach 4½ jähringer Krankheitsdauer tritt der Tod ein" (Alzheimer, 1907, p. 147).
2. "Eine weitere Besonderheit des vorliegenden Falles lag in der Lokalization der Veränderungen. Wenn es sich auch um eine diffuse Erkrankung der ganzen Rinde (abgesehen von dem übringen Zentralnervensystem) handelte, so waren doch unverkennbar beiderseits Scheitel- und Schläfenlappen besonders stark und stärker als das Stirnhirn betroffen. Bei den gewöhnlichen Fällen der senilen Demenz ist jedenfalls das Stirnhirn am erheblichsten erkrankt, wie das neuerdings auch wieder Simchowicz gefunden hat" (Alzheimer, 1911, p. 377).

REFERENCES

Abéley, X., Desclaux, P., Naudascher, J., & Suttel, R. (1945). Maladie d'Alzheimer avec atrophie frontale prédominante [Alzheimer's disease with predominant frontal atrophy]. *Annals Médico-Psychologiques*, *1*, 151–157.

Alzheimer, A. (1898). Neuer Arbeiten uber die dementia senilis und die auf atheromatoser Gefasserkrankung basierenden Gehirnkrankheiten [Newer studies on senile dementia and brain diseases caused by atheromatous vascular disease]. *Monatschrift für Psychiatrie und Neurologie*, *3*, 101–115.

Alzheimer, A. (1899). Beitrag zur pathologischen Anatomie der Seelenströrungen des Greisenalters [A contribution concerning the pathological anatomy of mental disturbances in old age]. *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin*, *56*, 272–273.

Alzheimer, A. (1899/1991). A contribution concerning the pathological anatomy of mental disturbances in old age. *Alzheimer Disease and Associated Disorders*, *5*, 69–70.

Alzheimer, A. (1906). Uber einen eigenartigen schweren Erkrankungsprozess der Hirnrinde [On an extraordinary, severe disease process of the cerebral cortex]. *Neurologisches Zentralblatt*, *25*, 1134.

Alzheimer, A. (1907). Ueber eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin*, *64*, 146–148.

Alzheimer, A. (1907/1987). A characteristic disease of the cerebral cortex. In K. Bick, L. Amaducci, & G. Pepeu (Eds.), *The early story of Alzheimer's disease*. New York: Raven.

Alzheimer, A. (1911). Ueber eigenartige Krankheitsfalle des spateren Alters. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, *4*, 356–385.

Alzheimer, A., Forstl, H., & Levy, R. (1911/1991). On certain peculiar diseases of old age. *History of Psychiatry*, *2*, 71–101.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Ames, B. N., & Shigenaga, M. K. (1992). Oxidants are a major contributor to aging. *Annals of the New York Academy of Sciences*, *663*, 85–96.

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients in Alzheimer's disease. *Cerebral Cortex*, *1*, 103–116.

Assal, F., Alarcon, M., Solomon, E. C., Masterman, D., Geschwind, D. H., & Cummings, J. L. (2004). Association of the serotonin transporter and receptor gene polymorphisms in neuropsychiatric symptoms in Alzheimer disease. *Archives of Neurology*, *61*, 1249–1253.

Back-Madruga, C., Boone, K. B., Briere, J., Cummings, J., McPherson, S., Fairbanks, L., et al. (2002). Functional ability in executive variant Alzheimer's disease and typical Alzheimer's disease. *Clinical Neuropsychology*, *16*, 331–340.

Baddeley, A. D., Della Sala, S., & Spinnler, H. (1991). The two-component hypothesis of memory deficit in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *13*, 372–380.

Becker, J. T. (1988). Working memory and secondary memory deficits in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *10*, 739–753.

Becker, J. T., Bajulaiye, O., & Smith, C. (1992). Longi-

tudinal analysis of a two component model of the memory deficit in Alzheimer's disease. *Psychological Medicine*, *22*, 437–445.

Becker, J. T., Huff, R. J., Nebes, R. D., Holland, A., & Boller, F. (1988). Neuropsychological function in Alzheimer's disease: Pattern of impairment and rates of progression. *Archives of Neurology*, *45*, 263–268.

Benson, D. F. (1986). Alzheimer's disease: The pedigree. In A. B. Scheibel, A. F. Wechsler, & M. A. B. Brazier (Eds.), *The biological substrates of Alzheimer's disease* (pp. 1–7). New York: Academic Press.

Berlin, L. (1949). Presenile sclerosis (Alzheimer's disease) with features resembling Pick's disease. *Archives of Neurology and Psychiatry*, *61*, 369–384.

Binetti, G., Magni, E., Padovani, S., Cappa, S. F., Bianchetti, A., & Trabucchi, M. (1996). Executive dysfunction in early Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *60*, 91–93.

Black, S. E. (1996). Focal cortical atrophy syndromes. *Brain and Cognition*, *31*, 188–229.

Bokde, A. L., Pietrini, P., Ibanez, V., Furey, M. L., Alexander, G. E., Graff-Radford, N. R., et al. (2001). The effect of brain atrophy on cerebral hypometabolism in the visual variant of Alzheimer disease. *Archives of Neurology*, *58*, 480–486.

Bonfiglio, F. (1908/1987). Concerning special findings in a case of probable cerebral syphilis. In K. Bick, L. Amaducci, & G. Pepeu (Eds.), *The early story of Alzheimer's disease* (pp. 19–31). New York: Raven.

Boyle, P. A., Malloy, P. F., Salloway, S., Cahn-Weiner, D. A., Cohen, R., & Cummings, J. L. (2003). Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *American Journal of Geriatric Psychiatry*, *11*, 214–221.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*, 239–259.

Braak, H., & Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging*, *16*, 271–284.

Brun, A. (1987). Frontal lobe degeneration of non-Alzheimer type: I. Neuropathology. *Archives of Gerontology and Geriatrics*, *6*, 193–208.

Brun, A., & Englund, E. (1981). Regional pattern of degeneration in Alzheimer's disease: Neuronal loss and histopathological grading. *Histopathology*, *5*, 549–564.

Brun, A., & Englund, E. (1986). A white matter disorder in dementia of the Alzheimer type: A pathoanatomical study. *Annals of Neurology*, *19*, 253–262.

Brun, A., & Gustafson, L. (1976). Distribution of cerebral degeneration in Alzheimer's disease: A clinicopathological study. *Archiv für Psychiatrie und Nervenkrankheiten*, *223*, 15–33.

Brun, A., & Gustafson, L. (1978). Limbic lobe involvement in presenile dementia. *Archiv für Psychiatrie und Nervenkrankheiten*, *226*, 79–93.

Brun, A., Gustafson, L., & Ingvar, D. H. (1975). Neuropathological findings related to neuropsychiatric symptoms and regional cerebral blood flow in presenile dementia. In *VIIth International Congress of Neuropathology* (pp. 101–105). Amsterdam: Excerpta Medica.

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron*, *44*(1), 195–208.

Celsis, P., Agniel, A., Puel, M., Rascol, A., & Marc-Vergnes, J. P. (1987). Focal cerebral hypoperfusion and selective cognitive deficit in dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery, and Psychiatry*, *50*, 1602–1612.

Chase, T. N., Foster, N. L., Fedio, P., Brooks, R., Mansi, L., & Di Chiro, G. (1984). Regional cortical dysfunction in Alzheimer's disease as determined by positron emission tomography. *Annals of Neurology*, *15*(Suppl.), S170–S174.

Chen, S. T., Sultzer, D. L., Hinkin, C. H., Mahler, M. E., & Cummings, J. L. (1998). Executive dysfunction in Alzheimer's disease: Association with neuropsychiatric symptoms and functional impairment. *Journal of Neuropsychiatry and Clinical Neurosciences*, *10*, 426–432.

Chlopicki, K., & Rzewuska-Szatowska, M. (1971). [Differential diagnosis in Alzheimer–Pick disease]. *Psychiatria Polska*, *5*, 363–366.

Chui, H. C., Teng, E. L., Henderson, V. W., & Moy, A. C. (1985). Clinical subtypes of dementia of the Alzheimer type. *Neurology*, *35*, 1544–1550.

Collette, F., Van der Linden, M., Delrue, G., & Salmon, E. (2002). Frontal hypometabolism does not explain inhibitory dysfunction in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *16*, 228–238.

Collette, F., Van der Linden, M., & Salmon, E. (1999). Executive dysfunction in Alzheimer's disease. *Cortex*, *35*, 57–72.

Craig, A. H., Cummings, J. L., Fairbanks, L., Itti, L., Miller, B. L., Li, J., et al. (1996). Cerebral blood flow correlates of apathy in Alzheimer disease. *Archives of Neurology*, *53*, 1116–1120.

Craig, D., Hart, D. J., Carson, R., McIlroy, S. P., & Passmore, A. P. (2004). Allelic variation at the A218C tryptophan hydroxylase polymorphism influences agitation and aggression in Alzheimer's disease. *Neuroscience Letters*, *363*, 199–202.

Craig, D., Hart, D. J., McCool, K., McIlroy, S. P., & Passmore, A. P. (2004). Apolipoprotein E ε4 allele influences aggressive behaviour in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*, 1327–1330.

Crystal, H. A., Horoupian, D. S., Katzman, R., & Jotkowitz, S. (1982). Biopsy-proved Alzheimer disease presenting as a right parietal lobe syndrome. *Annals of Neurology*, *12*, 186–188.

Cummings, J. L. (1998). Frontal–subcortical circuits and human behavior. *Journal of Psychosomatic Research*, *44*, 627–628.

Cummings, J. L. (2000). Cognitive and behavioral heterogeneity in Alzheimer's disease: Seeking the neuro-

biological basis. *Neurobiology of Aging*, *21*, 845–861.

Cummings, J. L., & Back, C. (1998). The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *American Journal of Geriatric Psychiatry*, *6*, S64–S78.

Cummings, J. L., & Benson, D. F. (1992). *Dementia: A clinical approach*. Boston: Butterworth-Heinemann.

de Groot, J. C., de Leeuw, F. E., Oudkerk, M., van Gijn, J., Hofman, A., Jolles, J., et al. (2000). Cerebral white matter lesions and cognitive function: The Rotterdam Scan Study. *Annals of Neurology*, *47*(2), 145–151.

Delay, J., & Brion, S. (1962). *Les démences tardives* [Late-onset dementia]. Paris: Masson.

Dermaut, B., Kumar-Singh, S., Engelborghs, S., Theuns, J., Rademakers, R., Saerens, J., et al. (2004). A novel presenilin 1 mutation associated with Pick's disease but not beta-amyloid plaques. *Annals of Neurology*, *55*, 617–626.

Detoledo-Morrell, L., Sullivan, M. P., Morrell, F., Wilson, R. S., Bennett, D. A., & Spencer, S. (1997). Alzheimer's disease: *In vivo* detection of differential vulnerability of brain regions. *Neurobiology of Aging*, *18*, 463–468.

Divry, P., Ley, J., & Titeca, J. (1935). Maladie d'Alzhiemer avec atrophie frontale predominante [Alzheimer's disease with predominant frontal atrophy]. *Journal Belge de Neurologie et de Psychiatrie*, *35*, 495–507.

Duke, L. M., & Kaszniak, A. W. (2000). Executive control functions in degenerative dementias: A comparative review. *Neuropsychology Review*, *10*, 75–99.

Faden, A. I., & Townsend, J. J. (1976). Myoclonus in Alzheimer's disease. *Archives of Neurology*, *33*, 278–280.

Fischer, O. (1907/1987). Miliary necrosis with nodular proliferation of the neurofibrils, a common change of the cerebral cortex in senile dementia. In K. Bick, L. Amaducci, & G. Pepeu (Eds.), *The early story of Alzheimer's disease* (pp. 5–18). New York: Raven.

Forstl, H., Burns, A., Levy, R., & Cairns, N. (1994). Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *British Journal of Psychiatry*, *165*, 53–59.

Foster, N. L., Chase, T. N., Fedio, P., Patronas, N. J., Brooks, R. A., & Di Chiro, G. (1983). Alzheimer's disease: Focal cortical changes shown by positron emission tomography. *Neurology*, *33*, 961–965.

Friedland, R. P., Koss, E., Haxby, J. V., Grady, C. L., Luxenberg, J., Schapiro, M. B., et al. (1988). NIH conference: Alzheimer disease: Clinical and biological heterogeneity. *Annalso of Internal Medicine*, *109*, 298–311.

Galton, C. J., Patterson, K., Xuereb, J. H., & Hodges, J. R. (2000). Atypical and typical presentations of Alzheimer's disease: A clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain*, *123*(3), 484–498.

Goldman, J. S., Johnson, J. K., McElligott, K., Suchowersky, O., Miller, B. L., & Van Deerlin, V. M. (2005). The presenilin 1 Glu318Gly polymorphism: Interpret with caution. *Archives of Neurology*, *62*, 1624–1627.

Grady, C. L., Haxby, J. V., Horwitz, B., Sundaram, M., Berg, G., Schapiro, M., et al. (1988). Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. *Journal of Clinical and Experimental Neuropsychology*, *10*, 576–596.

Grady, C. L., Haxby, J. V., Schapiro, M. B., Gonzalez-Aviles, A., Kumar, A., Ball, M. J., et al. (1990). Subgroups in dementia of the Alzheimer type identified using positron emission tomography. *Journal of Neuropsychiatry and Clinical Neurosciences*, *2*, 373–384.

Gustafson, L. (1987). Frontal lobe degeneration of non-Alzheimer type: II. Clinical picture and differential diagnosis. *Archives of Gerontology and Geriatrics*, *6*, 209–223.

Gustafson, L., Brun, A., & Ingvar, D. H. (1977). Clinical and neurocirculatory findings in presenile dementia related to neuropathological changes. *Activitas Nervosa Superior*, *19*(Suppl. 2), 351–353.

Gustafson, L., Hagberg, B., Holley, J. W., Risberg, J., & Ingvar, D. H. (1970). Regional cerebral blood flow in organic dementia with early onset: Correlations with psychiatric symptoms and psychometric variables. *Acta Neurologica Scandinavica*, *46*(Suppl. 43), 74–45.

Haas, C., Hung, A. Y., & Selkoe, D. J. (1991). Processing of beta-amyloid precursor protein in microglia and astrocytes favors an internal localization over constitutive secretion. *Journal of Neuroscience*, *11*, 3783–3793.

Haxby, J. V., Duara, R., Grady, C. L., Cutler, N. R., & Rapoport, S. R. (1985). Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism*, *5*, 193–200.

Haxby, J. V., Grady, C. L., Koss, E., Horwitz, B., Schapiro, M., Friedland, M. P. et al. (1988). Heterogeneous anterior–posterior metabolic patterns in dementia of the Alzheimer type. *Neurology*, *38*, 1853–1863.

Hirono, N., Mega, M. S., Dinov, I. D., Mishkin, F., & Cummings, J. L. (2000). Left frontotemporal hypoperfusion is associated with aggression in patients with dementia. *Archives of Neurology*, *57*, 861–866.

Hodges, J. R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease?: Neuroanatomical and diagnostic implications. *Neuropsychologia*, *33*, 441–459.

Hof, P. R., Bouras, C., Constantinidis, J., & Morrison, J. H. (1989). Balint's syndrome in Alzheimer's disease: Specific disruption of the occipito-parietal visual pathway. *Brain Research*, *493*, 368–375.

Hof, P. R., Bouras, C., Constantinidis, J., & Morrison, J. H. (1990). Selective disconnection of specific visual association pathways in cases of Alzheimer's disease

presenting with Balint's syndrome. *Journal of Neuropathology and Experimental Neurology*, *49*, 168–184.

Holmes, C., Arranz, M. J., Powell, J. F., Collier, D. A., & Lovestone, S. (1998). 5-HT_{2A} and 5-HT_{2C} receptor polymorphisms and psychopathology in late onset Alzheimer's disease. *Human Molecular Genetics*, *7*, 1507–1509.

Honer, W. G., Dickson, D. W., Gleeson, J., & Davies, P. (1992). Regional synaptic pathology in Alzheimer's disease. *Neurobiology of Aging*, *13*(3), 375–382.

Ingvar, D., Obrist, W., Chivian, E., Cronquist, S., Risberg, J., Gustafson, L., et al. (1968). General and regional abnormalities of cerebral blood flow in senile and "presenile" dementia. *Scandinavian Journal of Clinical and Laboratory Investigation: Supplement*, *102*, XII:B.

Johnson, J. K., Head, E., Kim, R., Starr, A., & Cotman, C. W. (1999). Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Archives of Neurology*, *56*, 1233–1239.

Johnson, J. K., Vogt, B. A., Kim, R., Cotman, C. W., & Head, E. (2004). Isolated executive impairment and associated frontal neuropathology. *Dementia and Geriatric Cognitive Disorders*, *17*, 360–367.

Kanne, S. M., Balota, D. A., Storandt, M., McKeel, D. W., Jr., & Morris, J. C. (1998). Relating anatomy to function in Alzheimer's disease: Neuropsychological profiles predict regional neuropathology 5 years later. *Neurology*, *50*, 979–985.

Katzman, R., & Bick, K. (2000). *Alzheimer disease: The changing view.* San Diego, CA: Academic Press.

Kirshner, H. J., Webb, W. G., Kelly, M. P., & Wells, C. E. (1984). Language disturbance: An initial symptom of cortical degenerations and dementia. *Archives of Neurology*, *41*, 491–496.

Kramer, J., & Miller, B. (2000). Alzheimer's disease and its focal variants. *Seminars in Neurology*, *20*, 447–454.

Kreindler, A., Hornet, T., & Appel E. (1959). Complex forms of cerebral senility. *Rumanian Medical Review*, *3*, 43–47.

Kuzis, G., Sabe, L., Tiberti, C., Dorrego, F., & Starkstein, S. E. (1999). Neuropsychological correlates of apathy and depression in patients with dementia. *Neurology*, *52*, 1403–1407.

Laflèche, G., & Albert, M. S. (1995). Executive function deficits in mild Alzheimer's disease. *Neuropsychology*, *9*, 313–320.

Lange, K. L., Bondi, M. W., Salmon, D. P., Galasko, D., Delis, D. C., Thomas, R. G., et al. (2002). Decline in verbal memory during preclinical Alzheimer's disease: Examination of the effect of APOE genotype. *Journal of the International Neuropsychological Society*, *8*, 943–955.

Lauter, H. (1970). Über spätformen der Alzheimerschen Krankheit und ihre Beziehung zur senilen Demenz [Late forms of Alzheimer's disease and their relationship to senile dementia]. *Psychiatria Clinica*, *3*, 169–189.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Liebers, M. (1939). Alzheimersche Krankheit mit Pickscher Atrophie der Stirnlappen. *Archiv für Psychiatrie und Nervenkrankheiten*, *109*, 363–370.

Liu, X., & Brun, A. (1995). Synaptophysin immunoreactivity is stable 36 h postmortem. *Dementia*, *6*, 211–217.

Liu, X., Erikson, C., & Brun, A. (1996). Cortical synaptic changes and gliosis in normal aging, Alzheimer's disease and frontal lobe degeneration. *Dementia*, *7*(3), 128–134.

Lopez, O. L., Becker, J. T., Klunk, W., Saxton, J., Hamilton, R. L., Kaufer, D. I., et al. (2000). Research evaluation and diagnosis of possible Alzheimer's disease over the last two decades: II. *Neurology*, *55*, 1863–1869.

Lu, T., Pan, Y., Kao, S.-Y., Li, C., Kohane, I., Chan, J., et al. (2004). Gene regulation and DNA damage in the ageing human brain. *Nature*, *429*, 883–891.

Madden, D. J., Whiting, W. L., Huettel, S. A., White, L. E., MacFall, J. R., & Provenzale, J. M. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: Relation to response time. *NeuroImage*, *21*(3), 1174–1181.

Mann, U. M., Mohr, E., Gearing, M., & Chase, T. N. (1992). Heterogeneity in Alzheimer's disease: Progression rate segregated by distinct neuropsychological and cerebral metabolic profiles. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*, 956–959.

Martin, A. (1990). Neuropsychology of Alzheimer's disease: The case for subgroups. In M. F. Schwartz (Ed.), *Modular deficits in Alzheimer's type dementia* (pp. 145–175). Cambridge, MA: MIT Press.

Martin, A., Brouwers, P., Lalonde, F., Cox, C., Teleska, P., Fedio, P., et al. (1986). Towards a behavioral typology of Alzheimer's patients. *Journal of Clinical and Experimental Neuropsychology*, *8*, 594–610.

Masliah, E., Mallory, M., Hansen, L., DeTeresa, R., & Terry, R. D. (1993). Quantitative synaptic alterations in the human neocortex during normal aging. *Neurology*, *43*(1), 192–197.

Masliah, E., Rockenstein, E., Veinbergs, I., Sagara, Y., Mallory, M., Hashimoto, M., et al. (2001). Beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 12245–12250.

Mayeux, R., Stern, Y., & Spanton, S. (1985). Heterogeneity in dementia of the Alzheimer type: Evidence of subgroups. *Neurology*, *35*, 453–461.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*, 939–944.

McPherson, S., Fairbanks, L., Tiken, S., Cummings, J.

L., & Back-Madruga, C. (2002). Apathy and executive function in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *8*, 373–381.

Mega, M. S., Lee, L., Dinov, I. D., Mishkin, F., Toga, A. W., & Cummings, J. L. (2000). Cerebral correlates of psychotic symptoms in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *69*, 167–171.

Minoshima, S., Foster, N. L., & Kuhl, D. E. (1994). Posterior cingulate cortex in Alzheimer's disease [Letter]. *Lancet*, *344*, 895.

Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L., & Kuhl, D. E. (1997). Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Annals of Neurology*, *42*, 85–94.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., et al. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology*, *58*, 397–405.

Morrison, J. H., & Hof, P. R. (2002). Selective vulnerability of corticocortical and hippocampal circuits in aging and Alzheimer's disease. *Progress in Brain Research*, *136*, 467–486.

Moyano, B. A. (1932). I. Enfermedad de Alzeimer II: Atrofia de Pick [Alzheimer's disease II: Pick atrophy]. *Archivos argentinos de Neurologia*, *7*, 231–286.

Nacmias, B., Tedde, A., Forleo, P., Piacentini, S., Guarnieri, B. M., Bartoli, A., et al. (2001). Association between 5-HT(2A) receptor polymorphism and psychotic symptoms in Alzheimer's disease. *Biological Psychiatry*, *50*, 472–475.

Nebes, R. D., & Brady, C. B. (1989). Focused and divided attention in Alzheimer's disease. *Cortex*, *25*, 305–315.

Nestor, P. G., Parasuraman, R., Haxby, J. V., & Grady, C. L. (1991). Divided attention and metabolic brain dysfunction in mild dementia of the Alzheimer's type. *Neuropsychologia*, *29*, 379–387.

Nichols, N. R., Day, J. R., Laping, N. J., Johnson, S. A., & Finch, C. E. (1993). GFAP mRNA increases with age in rat and human brain. *Neurobiology of Aging*, *14*(5), 421–429.

Ojaimi, J., Masters, C. L., Opeskin, K., McKelvie, P., & Byrne, E. (1999). Mitochondrial respiratory chain activity in the human brain as a function of age. *Mechisms of Ageing and Development*, *111*(1), 39–47.

O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*, *57*(4), 632–638.

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review. *Brain*, *122*, 383–404.

Perry, R. J., & Hodges, J. R. (2000). Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. *Neurology*, *54*, 2277–2284.

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: Relationship to episodic and semantic memory impairment. *Neuropsychologia*, *38*, 252–271.

Perusini, G. (1909). Uber klinisch und histologisch eigenartige psychische Erkrankungen des spateren Lebensalters. *Histologische und histopathologische Arbeiten uber die Grosshirnrinde*, *3*, 297–358.

Perusini, G. (1909/1987). Histology and clinical findings of some psychiatric diseases of older people. In K. Bick, L. Amaducci, & G. Pepeu (Eds.), *The early story of Alzheimer's disease* (pp. 82–128). New York: Raven.

Pietrini, P., Furey, M. L., Graff-Radford, N., Freo, U., Alexander, G. E., Grady, C. L., et al. (1996). Preferential metabolic involvement of visual cortical areas in a subtype of Alzheimer's disease: Clinical implications. *American Journal of Psychiatry*, *153*, 1261–1268.

Pillon, B., Dubois, B., Lhermitte, F., & Agid, Y. (1986). Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. *Neurology*, *36*, 1179–1185.

Pogacar, S., & Williams, R. S. (1984). Alzheimer's disease presenting as slowly progressive aphasia. *Rhode Island Medical Journal*, *67*, 181–185.

Raux, G., Gantier, R., Thomas-Anterion, C., Boulliat, J., Verpillat, P., Hannequin, D., et al. (2000). Dementia with prominent frontotemporal features associated with L113P presenilin 1 mutation. *Neurology*, *55*, 1577–1578.

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., & Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: Evidence from structural magnetic resonance imaging. *Neuropsychology*, *12*(1), 95–114.

Razani, J., Boone, K. B., Miller, B. L., Lee, A., & Sherman, D. (2001). Neuropsychological performance of right- and left-frontotemporal dementia compared to Alzheimer's disease. *Journal of the International Neuropsychological Society*, *7*, 468–480.

Rothschild, D., & Kasanin, J. (1936). Clinicopathological study of Alzheimer's disease: Relationship to senile conditions. *Archives of Neurology and Psychiatry*, *36*, 293–321.

Sarazin, M., Michon, A., Pillon, B., Samson, Y., Canuto, A., Gold, G., et al. (2003). Metabolic correlates of behavioral and affective disturbances in frontal lobe pathologies. *Journal of Neurology*, *250*, 827–833.

Seitelberger, F., & Jellinger, K. (1958). Umschriebene Grosshirnatrophie bei Alzheimerscher Krankheit [Circumscribed cerebral atrophy in Alzheimer's disease]. *Deutsche Zeitschrift für Nervenheilkunde*, *178*, 365–379.

Sgaramella, T. M., Borgo, F., Mondini, S., Pasini, M., Toso, V., & Semenza, C. (2001). Executive deficits appearing in the initial stage of Alzheimer's disease. *Brain and Cognition*, *46*, 264–268.

Simchowicz, T. (1910). Histologische Studien uber die senile Demenz. *Histologische und Histopathologische Arbeiten uber die Grosshirnrinde*, *4*, 267–444.

Sjogren, T., Sjogren, H., & Lindgren, A. G. (1952). Morbus Alzheimer and morbus Pick; a genetic, clinical and patho-anatomical study. *Acta Psychiatrica et Neurologica Scandinavica*, *82*, 1–152.

Stout, J. C., Wyman, M. F., Johnson, S. A., Peavy, G. M., & Salmon, D. P. (2003). Frontal behavioral syndromes and functional status in probable Alzheimer disease. *American Journal of Geriatric Psychiatry*, *11*, 683–686.

Stuss, D. T., & Knight, R. T. (2002). *Principles of frontal lobe function*. Oxford, UK: Oxford University Press.

Sukonick, D. L., Pollock, B. G., Sweet, R. A., Mulsant, B. H., Rosen, J., Klunk, W. E., et al. (2001). The 5-HTTPR*S/*L polymorphism and aggressive behavior in Alzheimer disease. *Archives of Neurology*, *58*, 1425–1428.

Sultzer, D. L., Brown, C. V., Mandelkern, M. A., Mahler, M. E., Mendez, M. F., Chen, S. T., et al. (2003). Delusional thoughts and regional frontal/temporal cortex metabolism in Alzheimer's disease. *American Journal of Psychiatry*, *160*, 341–349.

Sultzer, D. L., Mahler, M. E., Mandelkern, M. A., Cummings, J. L., Van Gorp, W. G., Hinkin, C. H., et al. (1995). The relationship between psychiatric symptoms and regional cortical metabolism in Alzheimer's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *7*, 476–484.

Swanberg, M. M., Tractenberg, R. E., Mohs, R., Thal, L. J., & Cummings, J. L. (2004). Executive dysfunction in Alzheimer disease. *Archives of Neurology*, *61*, 556–560.

Sweet, R. A., Hamilton, R. L., Lopez, O. L., Klunk, W. E., Wisniewski, S. R., Kaufer, D. I., et al. (2000). Psychotic symptoms in Alzheimer's disease are not associated with more severe neuropathologic features. *International Psychogeriatrics*, *12*, 547–558.

Talbot, K., Young, R. A., Jolly-Tornetta, C., Lee, V. M., Trojanowski, J. Q., & Wolf, B. A. (2000). A frontal variant of Alzheimer's disease exhibits decreased calcium-independent phospholipase A2 activity in the prefrontal cortex. *Neurochemistry International*, *37*, 17–31.

Tang-Wai, D., Lewis, P., Boeve, B., Hutton, M., Golde, T., Baker, M., et al. (2002). Familial frontotemporal dementia associated with a novel presenilin-1 mutation. *Dementia and Geriatric Cognitive Disorders*, *14*, 13–21.

Tariska, I. (1970). Circumscribed cerebral atrophy in Alzheimer's disease: A pathological study. In G. E. W. Wolstenholme & M. O'connor (Eds.), *Alzheimer's disease and related conditions: A CIBA Foundation Symposium* (pp. 51–73). London: Churchill.

Tekin, S., Mega, M. S., Masterman, D. M., Chow, T., Garakian, J., Vinters, H. V., et al. (2001). Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. *Annals of Neurology*, *49*, 355–361.

Thal, D. R., Rub, U., Orantes, M., & Braak, H. (2002). Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*, *58*, 1791–1800.

Unger, J. W. (1998). Glial reaction in aging and Alzheimer's disease. *Microscopy Research and Technique*, *43*(1), 24–28.

Villareal, D. T., Grant, E., Miller, J. P., Storandt, M., McKeel, D. W., & Morris, J. C. (2003). Clinical outcomes of possible versus probable Alzheimer's disease. *Neurology*, *61*(5), 661–667.

Vogt, B. A., Martin, A., Vrana, K. E., Absher, J. R., Vogt, L. J., & Hof, P. R. (1999). Mutifocal cortical neurodegeneration in Alzheimer's disease. *Cerebral Cortex*, *14*, 553–601.

Vogt, B. A., Vogt, L. J., & Hof, P. R. (2001). Patterns of cortical neurodegeneration in Alzheimer's disease: Subgroups, subtypes, and implications for staging strategies. In P. R. Hof & C. V. Mobbs (Eds.), *Functional neurobiology of aging* (pp. 111–129). San Diego, CA: Academic Press.

Waldemar, G., Bruhn, P., Kristensen, M., Johnsen, A., Paulson, O. B., & Lassen, N. A. (1994). Heterogeneity of neocortical cerebral blood flow deficits in dementia of the Alzheimer type: A [^{99m}Tc]-d,l-HMPAO SPECT study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *57*, 285–295.

Wang, D. S., Bennett, D. A., Mufson, E., Cochran, E., & Dickson, D. W. (2004). Decreases in soluble alpha-synuclein in frontal cortex correlate with cognitive decline in the elderly. *Neuroscience Letters*, *359*, 104–108.

Wang, D. S., Bennett, D. A., Mufson, E. J., Mattila, P., Cochran, E., & Dickson, D. W. (2004). Contribution of changes in ubiquitin and myelin basic protein to age-related cognitive decline. *Neuroscience Research*, *48*, 93–100.

Welsh, K., Butters, N., Hughes, J., Mohs, R., & Heyman, A. (1991). Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. *Archives of Neurology*, *48*, 278–281.

Yao, P. J., Zhu, M., Pyun, E. I., Brooks, A. I., Therianos, S., Meyers, V. E., et al. (2003). Defects in expression of genes related to synaptic vesicle trafficking in frontal cortex of Alzheimer's disease. *Neurobiology of Disease*, *12*, 97–109.

Zubenko, G. S., Moossy, J., Martinez, A. J., Rao, G., Claassen, D., Rosen, J., et al. (1991). Neuropathologic and neurochemical correlates of psychosis in primary dementia. *Archives of Neurology*, *48*, 619–624.