The Neuropsychology of Cortical Dementias
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The Neuropsychology of Cortical Dementias

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I dedicate this to my grandparents, Forrest and Ruth Noggle. Like many other families, mine came face-to-face with the realities of dementia when my grandmother was diagnosed with Alzheimer’s disease—CAN

To my children with all my heart—RSD
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Preface

Today the fastest-growing segment of our population is persons aged 65 and older. With advances in medical technologies and interventions, the average human life span has increased dramatically over the past several decades. We have seen a subsequent increase in the number of individuals developing dementia in some form as the risk for almost every primary dementing process increases with increasing age. Dementia, itself, does not describe a specific disease entity; rather, the term refers to a clinical syndrome that negatively affects an individual’s ability to participate in normal activities and relationships due to impaired cognitive functioning. The underlying cause and/or point of anatomical origin oftentimes dictates the specific clinical constellation observed.

Given the growing number of individuals developing dementia, scientific and clinical advances are constantly in demand. Neuropsychology has taken its place at the forefront of this movement. Professional neuropsychologists as well as those in training must remain up to date with the changing landscape that is the practice and science of assessing, diagnosing, and treating dementia.

The goal of The Neuropsychology of Cortical Dementias is to discuss the most recent advances in our understanding of this group of disorders and disease processes. Intended to advance clinical skills of professionals and trainees alike, this text covers the most advanced practices and techniques in early differential diagnosis, assessment, and treatment. The book focuses on cortical dementias as opposed to also discussing subcortical dementias. This permits a more in-depth discussion of individual types of cortical dementia, allowing for coverage of the most contemporary findings on the subject matter. This text discusses the foundations of neuropsychology in the assessment, diagnosis, and treatment of cortical dementias. Individual dementing processes are discussed in detail, from traditional presentations such as Alzheimer’s disease and Lewy body dementia to less commonly discussed entities such as primary progressive aphasia and chronic traumatic encephalopathy. Advances in neuroimaging and the utilization of biomarkers in early detection are discussed. Additional chapters are dedicated to related topics including the role of caregivers and determination of capacity. In all, the text offers a contemporary and comprehensive coverage of the subject matter that will be immediately applicable to scientists and clinicians alike, regardless of their level of training.
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The Neuropsychology of Psychopathology
The Neuropsychology of Cancer and Oncology
Neuropsychological Rehabilitation
The Neuropsychology of Cortical Dementias
The Neuropsychology of Pervasive Developmental Disorders
The Neuropsychology of Psychopharmacology
Foundations and Principles
The Neuroscience of Cortical Dementias: Linking Neuroanatomy, Neurophysiology, and Neuropsychology

Daniel A. Nation, David P. Salmon, and Mark W. Bondi

Dementia is a clinical syndrome characterized by the impairment of multiple cognitive domains that is severe enough to interfere with one’s usual social and occupational functioning. The impairment must represent a decline from a previously higher level of functioning and not occur exclusively during the course of delirium. According to widely applied diagnostic schemes (e.g., *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition—Text Revision* [DSM-IV-TR]; American Psychiatric Association, 2000), the cognitive impairment must include decline in memory and one or more of the following: aphasia, apraxia, agnosia, or executive dysfunction. Although these criteria are widely used in clinical and research settings, they have been criticized for being weighted toward the clinical features of dementia due to Alzheimer’s disease (AD), particularly because they require decline in memory and lack emphasis on neurobehavioral symptoms. This weighting can make it difficult to diagnose dementia in non-AD neurodegenerative disorders that cause profound losses of functional capacity due primarily to personality changes and behavioral deficits without decline in memory and, in some cases, only minimal decline in other cognitive domains. These limitations have led to the recent development of broader conceptualizations of dementia that account for the heterogeneous nature of clinical presentations (Ganguli & Rodriguez, 2011).

The clinical heterogeneity of dementia is a reflection of the variety of neurodegenerative diseases and neuropathological substrates that can give rise to the syndrome. Neuropsychological research that has taken a comparative approach to the study of various dementing disorders has shown that etiologically and neuropathologically distinct neurodegenerative diseases engender different patterns of relatively preserved and impaired cognitive abilities. This has been most clearly shown through the comparison of dementia syndromes associated with neurodegenerative diseases that primarily involve regions of the cerebral cortex (e.g., AD, frontotemporal dementia [FTD]) and those that have their primary locus in subcortical brain structures (e.g., Huntington’s disease [HD], Parkinson’s disease [PD], progressive...
supranuclear palsy [PSP]). Although it is well known that pathological changes in these various disorders are not limited to either cortical or subcortical brain regions, the cortical-subcortical dementia distinction serves as a heuristically useful model for describing the pattern of neuropsychological deficits that are observed in these patient groups.

Our chapter describes the neuropsychological, neuroanatomical, and neurophysiological features of several of the more common “cortical dementias.” These conditions primarily impact the association cortices and related limbic system structures (e.g., hippocampus, amygdala, cingulate cortex). We will first review AD, the most common form of dementia, and then compare and contrast the features of AD with those of other disorders that involve significant cortical pathology including dementia with Lewy bodies (DLB), FTD, and cortical vascular dementia (VaD). All of these disorders involve the selective targeting of “large-scale” cortical neuroanatomical networks, but they present with distinct neuropsychological profiles that are consistent with the anatomical locus of cortical neuropathology (Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Weintraub & Mesulam, 1993, 2009; Weintraub & Mesulam, 1996). For quick reference, a table is provided near the end of this chapter containing shorthand descriptions of the typical disease onset, course, neuropsychology, neuroimaging, and neuropathology associated with each cortical dementia syndrome (see Table 1.1).

**ALZHEIMER’S DISEASE**

AD is an age-related neurodegenerative disease characterized by the abnormal extracellular accumulation of amyloid in diffuse and senile plaques, the abnormal formation of tau-protein positive neurofibrillary tangles in neurons, cortical atrophy with associated neuron and synapse loss, and alterations in neurogenesis (Crews & Masliah, 2010; Masliah & Salmon, 1999). These neuropathological changes usually occur first in medial temporal lobe (MTL) structures such as the entorhinal cortex and hippocampus, and then advance to anterior and lateral cortical areas such as the basal forebrain and frontal and temporal lobe association cortices. Eventually, the pathology occurs in association cortices in the parietal and occipital lobes (Braak & Braak, 1991). The primary sensory and motor cortex usually remains free of AD pathology, with the exception of the olfactory cortex (Pearson, Esiri, Hiorns, Wilcock, & Powell, 1985). Subcortical structures (e.g., thalamus, basal ganglia) and cerebellum are also relatively spared, making AD a classic form of diffuse cortical dementia.

The development of cognitive deterioration associated with AD mirrors this temporal sequence of neuropathological changes. In the earliest stages of AD, patients often exhibit short-term memory loss and subtle executive dysfunction and semantic memory deficits (i.e., anomia and agnosia; Mickes et al., 2007) consistent with early MTL damage and marginal involvement of frontal and temporal cortices. As the disease progresses through frontal and temporal areas, memory deficits become severe and executive and language impairment becomes more prominent. Parietal areas may begin to be affected, leading to mild constructional deficits (i.e., apraxia) fairly early in the disease (Bondi et al., 2008). Patients may exhibit additional deficits in basic attention, abstract reasoning, and visuospatial abilities even during the relatively early stages of the disease (Salmon & Bondi, 2009). By the time moderate to severe stages of the disease are reached, all cortical association areas are substantially affected. These cognitive deficits may become profound.
Research focusing on the nature of the cognitive deficits found in patients with AD has improved our understanding of brain–behavior relationships by relating cognitive functions to the specific forms of neuropathology found in AD. This research has also provided a means of diagnosing the disease in the absence of any sufficiently sensitive and specific biomarkers. By examining the pattern and course of cognitive impairment that are characteristic of AD, neuropsychologists have provided a method for differentiating AD from other causes of dementia. Early diagnosis may have important clinical implications as disease-modifying therapies become available, and can be important for providing a prognosis, selecting symptom-based treatments, and planning for future care. This is particularly important given that AD is the most common cause of dementia, particularly in those older than 65 years, with an age of onset typically in the seventh and eighth decades of life. The incidence of AD increases with age and approximately 25% of individuals will have the disease by 85 years of age (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007).

The following sections review cognitive and neurophysiological research centered on understanding the brain–behavior mechanics involved in the cognitive deterioration associated with AD.

**Episodic Memory**

The most prominent and early clinical feature of AD is short-term episodic memory loss, characterized by a deficit in the ability to learn, store, and retrieve information that is newly acquired through personal experience. The learning and memory deficit present in AD patients involves both verbal and nonverbal (i.e., visual) memory and is characterized by “rapid forgetting” of recently acquired information (Salmon & Bondi, 2009). This deficit occurs in the context of normal attentional processes. AD patients show a failure to retain newly acquired information after a delay even when retrieval demands are reduced by use of a recognition format (Welsh, Butters, Hughes, Mohs, & Heyman, 1991).

The pattern of memory loss in AD stands in contrast to that of patients with subcortical neurodegeneration such as in HD. HD is an autosomal dominant genetic disorder characterized by degeneration of the neostriatum (caudate and putamen) with relative sparing of cortical tissues. HD patients develop a movement disorder (chorea), behavioral changes (e.g., depression, apathy), and progressive dementia (Vonsattel & DiFiglia, 1998). In contrast to AD, patients with HD exhibit learning and memory deficits on tests of free recall but show improved performance on recognition testing (Delis et al., 1991). This suggests that the memory deficit in HD patients may reflect retrieval dysfunction (Butters, Wolfe, Granholm, & Martone, 1986). This suggestion is consistent with research implicating frontostriatal circuits that are damaged in HD in working memory and the organization and retrieval of information from long-term storage. In contrast, the memory deficit observed in AD patients appears to reflect a failure to consolidate new information so that the information is never transferred from immediate working memory to a more permanent long-term storage (Tröster et al., 1993). Thus, the rapid forgetting of new information, together with the inability to retrieve that information despite the provision of a more structured recognition format, is characteristic of the episodic memory loss observed in AD.

Another important aspect of memory loss in patients with AD is retrograde amnesia (i.e., the inability to remember events that occurred prior to the onset of disease). The retrograde amnesia of AD is characterized by a temporal gradient in which recently acquired memories show greater impairment than more remotely acquired
memories. For example, Hodges, Salmon, and Butters (1993) showed that AD patients have a temporal gradient in terms of their ability to recognize famous people sampled from each decade of the patients’ lives, with famous people from earlier in their lives being better preserved than those from their more recent history.

This prominent episodic memory loss in AD is consistent with the early deterioration of MTL structures known to underlie the ability to form new memories (Squire, 1987). Specifically, patients in the early stages of AD show substantial neuropathological changes in the hippocampus, parahippocampal cortex, entorhinal cortex, and related cortical association areas that are responsible for the formation and consolidation of new memories (Squire, 1998). Degeneration begins in the entorhinal cortex, disconnecting the perforant pathway from the entorhinal cortex to the dentate gyrus of the hippocampus, and then includes intrahippocampal pathways connecting the dentate granular cells and CA3, CA1, and the subiculum (Hyman, Van Hoesen, & Damasio, 1987). These circuits integrating MTL structures are critical for the formation of new memories. In vivo evidence of MTL deafferentation can be visualized by structural neuroimaging studies, which have found that AD patients show hippocampal atrophy early in the course of disease and that these hippocampal changes are associated with memory disturbance (Deweer et al., 1995). Functional neuroimaging studies in AD patients and those at risk of AD have also demonstrated alterations in hippocampal cerebral blood flow and blood oxygen level dependent (BOLD) signal, both at rest and during new memory formation (Dai et al., 2009; Fleisher et al., 2005). Individuals with circumscribed lesions within these MTL structures display memory deficits that are similar to those found in AD, further implicating these structures in the episodic memory loss seen in AD patients (Albert, Butters, & Levin, 1979; Squire, 1998).

Reciprocal connections between the MTL structures and neocortical association areas throughout the brain are thought to underlie the process of new memory formation and consolidation (Dickerson & Eichenbaum, 2010). Specifically, neocortical areas send projections to the parahippocampal area, which sends projections back to these neocortical areas, and to other hippocampal sectors. These hippocampal projections follow a serial, unidirectional pathway from the dentate gyrus to CA3 and then on to CA1 and the subiculum, both of which then project back to the parahippocampal cortex (Eichenbaum, 2000). Plastic change of synaptic connections within the neocortical association areas is thought to be ultimately responsible for the storage of new information in long-term memory. The MTL structures are different from other cortical areas in that they have a selectively dedicated function to facilitate this memory consolidation process. Converging evidence from human and animal research suggests that after experience with a stimulus, specialized neurons within MTL structures play a role in matching a memory cue to a stored template of the stimulus in cortical association areas (Eichenbaum, 2004). Although the exact details of how the MTL forms new memories and retrieves them through coordination with cortical areas remain unclear, these highly specialized structures are critical to memory function.

Alzheimer’s pathology tends to most severely impact large glutaminergic pyramidal neurons in the entorhinal cortex and the CA1 and CA2 regions of the hippocampus (Masliah & Salmon, 1999). Damage to these large projecting neurons may profoundly impact signaling between MTL structures and disrupt the ability of these structures to coordinate signals with neocortical areas. Interruption of communication between MTL and neocortical areas necessary for the long-term synaptic change that underlies memory formation is likely to play a large role in the profound episodic memory loss observed in AD patients.
Semantic Memory

Semantic memory is distinct from episodic memory in that it is knowledge that is culturally shared, usually overlearned, and not temporally specific, whereas episodic memory is based on personal experiences that are time and place specific. Retrieval of semantic memories is less dependent on MTL function, as patients with circumscribed MTL lesions with profound episodic memory loss exhibit relatively intact semantic memory (Squire, 1998). In AD, there is substantial evidence for deficits in semantic memory that are distinct from their episodic memory deficits. For example, AD patients exhibit early deficits in semantic fluency (i.e., rapidly naming exemplars from a given category; Monsch et al., 1992) and confrontation naming (Mickes et al., 2007). In AD patients, spontaneous speech is often vague, empty of content words, and filled with indefinite phrases and circumlocutions (Nicholas, Obler, Albert, & Helm-Estabrooks, 1985). This breakdown in semantic memory is progressive, with the loss being more prominent in the later stages of the disease when a frank agnosia is present (Nebes, 1989). In fact, studies have shown that on tests of general semantic knowledge (e.g., the Number Information Test), which ask questions such as “How many days are in a year?” AD patient performance declines over the course of the disease (Norton, Bondi, Salmon, & Goodglass, 1997). Furthermore, patients are highly consistent in the items that they miss from year to year, suggesting a true loss of knowledge rather than a retrieval deficit. Loss of knowledge is also indicated by other studies that have found that when AD patients appear to have lost a concept (e.g., “horse”) on one particular test, this deficit is present across many tests and modes of access including spontaneous verbal production, confrontation naming, and the ability to properly sort the concept into the correct semantic category (e.g., “domestic animal”; Hodges, Salmon, & Butters, 1992).

Semantic memory is thought to be a cortical function that is not dependent on subcortical or limbic structures. In support of this notion, patients with subcortical forms of dementia, such as HD, do not exhibit deficits in semantic memory. Patients with HD may have generalized slowing that can reduce their verbal output on fluency tests, but they do not have disproportionate impairment (relative to normal controls) on fluency tasks that depend on semantic knowledge (i.e., produce as many animal names as possible in 1 minute) relative to those that do not (i.e., producing as many words that begin with the letter “F” as possible in 1 minute). In contrast, AD patients are significantly more impaired (relative to normal controls) on semantic fluency than phonemic fluency tasks (Henry, Crawford, & Phillips, 2004). These deficits may reflect the loss of semantic knowledge (i.e., general knowledge of facts, concepts, and the meanings or words) for particular items or concepts (Hodges & Patterson, 1995).

The semantic memory loss associated with AD is thought to be related to the degeneration of neocortical association areas of the temporal, frontal, and parietal lobes (Masliah, Miller, & Terry, 1993). Functional MRI (fMRI) and EEG studies have advanced our understanding of how semantic processing occurs in both normal and AD patients. Evidence from studying brain-damaged patients indicates that the organization, storage, and retrieval of semantic information involves a distributed network of neocortical and limbic areas, with particular reliance on posterior inferior parietal and inferotemporal regions (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004). A recent meta-analysis of fMRI studies in normal individuals concluded that semantic processing involves a variety of left-lateralizing cortical regions across all four brain lobes, but particularly the middle temporal gyrus, posterior inferior parietal lobe, dorsomedial prefrontal cortex, inferior frontal gyrus, ventromedial
frontal cortex, fusiform gyrus, cingulate gyrus, and the parahippocampal gyrus (Binder, Desai, Graves, & Conant, 2009). These studies attempt to parcel out the purely semantic aspects of language from simple lexical, syntactic, and phonological processes by contrasting the processing of meaningful words from nonwords. However, these methods are difficult to interpret given evidence from EEG and magnetoencephalography (MEG) experiments, indicating that the different components of language, including phonological, lexical, syntactic, and semantic processes, are performed in both serial and parallel circuits within temporal, parietal, and frontal regions (Pulvermüller, Shtyrov, & Hauk, 2009). There is also ongoing debate as to whether semantic information is stored in a modular fashion, with specific brain areas being dedicated to specific conceptual categories (e.g., living things vs. nonliving things), or in a distributed fashion based on attributes (e.g., furry vs. smooth; Done & Hajilou, 2005). Nevertheless, converging evidence implicates a variety of cortical areas, with special emphasis on parietal and temporal regions, both modular and distributed storage of attributes and categories, and both serial and parallel processing of semantic information in normal adults.

Fewer imaging studies have contrasted normal and AD participants on semantic processing tasks. In a recent study, Wierenga et al. used an fMRI-based semantic processing paradigm that allowed for examination of both modular (living vs. nonliving) and attribute (global vs. local) based semantic processing in normal older adults and AD patients (Wierenga et al., 2011). AD patients exhibited altered brain responses throughout a wide variety of frontal, temporal, and parietal brain regions irrespective of whether processing was modular or attribute based. These alterations suggest that semantic memory deficits in AD may be the result of generally abnormal and disorganized semantic processing throughout the distributed network of brain regions involved in storage of semantic information. Additional findings indicated that, during the task, AD patients recruited frontal regions within the right hemisphere that were not active in normal older adults. This observation suggests that AD patients may recruit additional brain regions not typically involved in semantic processing in order to compensate for their deficits, or that a failure to inhibit these unrelated brain regions may contribute to their processing deficits. Thus, the loss of semantic knowledge is thought to be related to the degradation of semantic network function represented within the higher cortical association areas that tend to be affected by AD.

Semantic memory involves integration of modular- and attribute-based representations across a variety of cortical areas through a cascade of serial and parallel circuits. This suggests that a high level of coordinated cortical activity may be required to effectively maintain and access semantic knowledge. Alzheimer’s pathology causes neuronal damage within neocortical layers that is partially selective for large glutamatergic pyramidal neurons (Masliah & Salmon, 1999). Clustering of neurofibrillary tangles in neurons within neocortical layers II and III is thought to result in disconnection of cortico-cortical fibers, which may lead to disruption of circuits responsible for communication both between and within cortical areas important for semantic processing (Esiri & Chance, 2006). Tangle clustering also occurs extensively within layer V neurons, potentially disrupting cortico-subcortical fibers that may indirectly sustain coordination of cortical activity through thalamic relay nuclei (Pearson et al., 1985). Together these findings support the cortico-cortical disconnection hypothesis of AD, which posits that neurofibrillary tangle and neuritic plaque formation causes neuronal dysfunction within cortical layers responsible for cellular communication across cortical regions (De Lacoste & White, 1993). The disconnection of cortical regions would impair functions that rely on distributed networks,
integration of storage modalities, and the ability to bind information obtained through parallel processing circuits, all of which appear to be involved in semantic memory. This is analogous but distinct from the disconnectivity that occurs early in the disease process between MTL structures and the neocortex, which results in loss of episodic memory.

**Executive Functions and Attention**

Deficits in executive and attentional abilities known to be related to frontal lobe function are observed in patients with AD (Collette, Schmidt, Scherrer, Adam, & Salmon, 2009). Executive deficits include difficulties with mental manipulation of information, concept formation, problem solving, and cue-directed behavior (Perry & Hodges, 1999; Perry, Watson, & Hodges, 2000). Specifically, AD patients are impaired on tasks requiring set-shifting, self-monitoring, and sequencing but not cue-directed attention or verbal problem solving. They show deficits on more difficult problem-solving tests, tests of relational integration, nonverbal abstract reasoning, and timed tests involving executive functions (Grady et al., 1988; Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Waltz et al., 2004). Deficits on specific tests of executive function such as those involving inhibition and switching have also been predictive of more global cognitive declines (Clark et al., 2012) or progression to dementia from mild cognitive impairment states in nondemented older adults (Brandt et al., 2009), although in general they may not be as sensitive to progression as episodic or semantic memory tasks (Aretouli, Ökonkwo, Samek, & Brandt, 2011; Mickes et al., 2007).

Deficits in complex executive functioning tasks may be due to neuronal damage within frontal lobe structures, as AD pathology spreads to these areas relatively early in the disease (Masliah et al., 1993). Another possible explanation for executive dysfunction is damage to forebrain areas supporting the acetylcholine diffuse activating system (Perry, Irving, & Perry, 1991). Forebrain regions, including the nucleus basalis of Meynert and the diagonal band of Broca, contain cholinergic neurons that project to a variety of cortical areas, including frontal regions known to be important in supporting higher executive abilities (e.g., prefrontal cortex; Schliebs & Arendt, 2006). The acetylcholine supplied by these diffuse activating systems is partly responsible for tonic activation of these regions during wakefulness. Thus, damage to forebrain regions should result in decreased activation of frontal regions and reduced ability to perform executive tasks. Acetylcholinesterase inhibitors (e.g., donepezil) are frequently prescribed during the early stages of AD to increase acetylcholine bioavailability through inhibition of the acetylcholine degrading enzyme (Cummings, 2000). If the acetylcholine depletion that results from basal forebrain damage is responsible for the executive function deficits observed early in the course of AD, then increased acetylcholine bioavailability should improve executive functions. In support of this hypothesis, a recent study found that the degree of acetylcholinesterase inhibition provided by donepezil treatment correlated with performance on attentional and executive tasks but not memory tasks in patients with mild AD (Bohnen et al., 2005). However, neuropathological studies have also separately linked tangle load within the basal forebrain to memory dysfunction in AD (Samuel, Terry, DeTeresa, Butters, & Masliah, 1994). Additionally, cholinergic receptor activity within frontal and anterior cingulate regions was predictive of future decline in executive function in AD patients (Colloby et al., 2010).

Other studies have found that decreased gray matter volume within the prefrontal and posterior inferior parietal cortex correlates with poor performance on executive function tasks in AD (Pa et al., 2010). These atrophic changes are likely related
to the underlying AD pathology, as neuropathological studies found that the loss of large pyramidal neurons within midfrontal regions correlates with performance on tests of global cognition (Masliah & Salmon, 1999). This association suggests that both neurodegenerative and neurochemical abnormalities within the prefrontal cortex may contribute to the executive dysfunction found in AD patients.

**Visuospatial Abilities**

Beyond the deficits in episodic memory, semantic memory, and executive function discussed previously, AD patients ultimately develop visuospatial processing deficits that are thought to be related to the encroachment of AD pathology on parietal, occipital, and ventral posterior temporal association areas. These deficits are not always present during the earliest stages of the disease but are present by the moderate stage of disease. This later appearance is consistent with neurofibrillary tangle and neuritic plaque progression that spares occipital and parietal regions in the early stages of disease, but ultimately engages all cortical association areas (Braak & Braak, 1991).

Visuospatial deficits in patients with AD are frequently apparent on visuoconstructional tasks such as the block design test (Padovani et al., 1995) and figure copy tests (Locascio, Growdon, & Corkin, 1995). Several studies have compared the visuospatial deficits found in AD to those found in subcortical dementia (e.g., HD). Patients with AD may be particularly impaired on tests that require processing of information presented in an extrapersonal orientation (Brouwers, Cox, Martin, Chase, & Fedio, 1984). This was shown on a task that examined the ability of AD and HD patients to perform mental rotation of visual stimuli (Lineweaver, Salmon, Bondi, & Corey-Bloom, 2005). Patients with AD were impaired at performing the mental rotation but did not show a reduction in speed when they were successful. In contrast, HD patients could perform mental rotation accurately, but showed a deficit in speed of processing consistent with bradyphrenia. The deficit in mental rotation exhibited by patients with AD suggests that they have dysfunction of cortical regions involved in processing visual motion. One such area, the middle temporal gyrus, typically has a heavy burden of AD pathology. On the other hand, it could be that deficits in extrapersonal orientation are due to disconnection between multiple cortical areas consistent with cortico-cortical disconnectivity.

Further evidence for cortico-cortical disconnectivity as the source of visuospatial impairment in AD comes from another study comparing AD and HD patients on a visual sensory integration task (Festa et al., 2005). In this task, subjects were required to detect the direction of coherently moving dots that could be distinguished from randomly moving distractor dots by color (red vs. green) or by luminance (light gray vs. dark gray). Both normal control subjects and HD patients were able to utilize color or luminance information to enhance their ability to detect the direction of motion of coherently moving dots. AD patients were able to utilize luminance information, but not color information to detect the direction of motion. This impairment suggests a deficit in the ability to bind motion and color information, which are processed in distinct cortical visual systems: the dorsal (magnocellular) visual processing stream for motion and the ventral (parvocellular) visual processing stream for color (Macko et al., 1982). In contrast, motion and luminance are both processed within the same dorsal visual processing stream. These findings suggest that the inability to bind information processed in distinct cortical pathways may underlie the visuospatial deficits observed in AD. This is consistent with the cortico-cortical disconnectivity hypothesis and points to a
general inability to bind information gathered from multiple cortical processing streams in AD.

More pronounced visuospatial deficits may be observed early in the posterior variant of AD, termed *posterior cortical atrophy* (PCA). PCA is a rare clinical dementia syndrome characterized by preserved memory, language, and insight with prominent visual agnosia (sometimes with prosopagnosia) and constructional apraxia. Patients may also exhibit many or all of the features of Balint’s syndrome, including optic ataxia, gaze apraxia, and simultanagnosia (i.e., can detect visual details of an object but cannot organize them into a meaningful whole). They may also exhibit many or all of the components of Gerstmann’s syndrome, including acalculia, right-left disorientation, finger agnosia, and agraphia (Caine, 2004). The condition is associated with atrophy and decreased blood flow to the occipital and posterior parietal cortex. PET studies have demonstrated metabolic derangement in posterior cortical areas, which may particularly impact the dorsal visual stream or “where” pathway (Nestor, Caine, Fryer, Clarke, & Hodges, 2003). The underlying neuropathology associated with this syndrome is frequently AD (i.e., neuritic plaques and neurofibrillary tangles), but may also occur with other neurodegenerative diseases. In cases where AD neuropathology is present, it exhibits the same laminar distribution within the cortex, suggesting the same mechanism of cortical damage as seen in the typical AD case (Hof, Vogt, Bouras, & Morrison, 1997).

**DEMENTIA WITH LEWY BODIES**

DLB is the second most common neurodegenerative cause of dementia (McKeith et al., 2004). This clinicopathological condition is characterized by a dementia syndrome that occurs in the presence of cell loss and the deposition of Lewy bodies in the brain. Lewy bodies are abnormal intracytoplasmic eosinophilic neuronal inclusion bodies that are comprised of alpha-synuclein- and ubiquitin-containing fibrillary aggregates (McKeith et al., 2005). In DLB, Lewy body pathology (including Lewy neurites) is distributed in a subcortical pattern similar to that of PD (e.g., in brain stem nuclei including the substantia nigra, locus ceruleus, dorsal motor nucleus of the vagus, and substantia innominata) and is also found diffusely distributed throughout the limbic system (e.g., cingulate, insula, amygdala, hippocampus, entorhinal cortex, and transentorhinal cortex) and neocortex. In limbic and neocortical regions, Lewy bodies typically involve the small neurons of the cortical layer V (Spillantini et al., 1997). In most cases, there is also AD pathology (i.e., neuritic plaques, neurofibrillary tangles) that occurs in the same general distribution throughout the brain as in “pure” AD (Gómez-Tortosa, Irizarry, Gómez-Isla, & Hyman, 2000).

The clinical presentation of DLB can be distinguished from that of PD based on the type of extrapyramidal signs and the course of these motor signs relative to cognitive decline. DLB patients tend to show cognitive deterioration at or before the onset of motor symptoms and show a more rapid cognitive decline, whereas PD patients typically present with motor signs of the disease for some number of years prior to the onset of cognitive decline if it occurs at all. Additionally, DLB patients are more likely to show axial signs, such as rigidity, masked facies, gait abnormalities, or postural instability, rather than lateral signs, such as resting tremor (McKeith et al., 2004). DLB may be distinguished from AD on the basis of the pattern of cognitive decline. DLB is characterized by a pattern of early severe executive and visuospatial impairment that is disproportionate to mild, retrieval-based memory impairment. This sharply contrasts with the typical AD presentation, which is characterized by early severe episodic memory impairment with milder executive dysfunction and
relatively preserved visuospatial abilities early in the disease (Simard, van Reekum, & Cohen, 2000). Other features that may help distinguish DLB from AD are its increased frequency of vivid well-formed visual hallucinations, rapid eye movement sleep behavior disorder, and fluctuations in cognition with pronounced variation in attention and alertness (McKeith et al., 2005).

Structural MRI studies often show diffuse cerebral cortical atrophy in DLB similar to that found in other forms of dementia (e.g., PD and AD; Watson, Blamire, & O’Brien, 2009), but a few studies suggest greater atrophy of frontal, parietal, and left occipital regions in DLB relative to AD or PD patients (Beyer, Larsen, & Aarsland, 2007; Whitwell et al., 2007). One challenge facing neuroimaging studies in DLB is selection of an adequate control group. Typically, DLB patients are compared with AD patients, PD patients with dementia, PD patients without dementia, normal controls, or all of these participant groups. This is because DLB patients may have both AD and Lewy body pathology; however, it is not possible to distinguish between DLB patients with and without comorbid AD pathology for these in vivo comparisons. This complicates interpretation of study findings.

It is a potentially important clinical problem to distinguish DLB from AD because they represent the two most common causes of neurodegenerative dementia, neither condition has a reliable biomarker, and they are known to have a different disease course and response to treatment that could alter quality of life and mortality. For instance, DLB patients are more likely than AD patients to show improved cognition in response to treatment with acetylcholinesterase inhibitors, but are also more likely to experience neuroleptic malignant syndrome, a potentially life-threatening condition, in response to antipsychotic medication (McKeith et al., 2005). Given the frequency with which treatment decisions are made concerning these medications in these highly prevalent forms of dementia, the differential diagnosis of DLB from AD is an important area of research. The present review focuses on cortically mediated cognitive deficits in visuospatial abilities, executive functions, and memory that may be most salient in differentiating DLB from AD.

Visuospatial Abilities

Although there are a number of clinical features that distinguish DLB from AD, the presence of visuospatial impairment has been found to be the best predictor of DLB pathology in autopsy-based studies (83% positive predictive value and 90% negative predictive value; Tiraboschi et al., 2006). The early and disproportionately severe visuospatial dysfunction found in patients with DLB may be detected on tests of basic visuoperceptual abilities (Calderon et al., 2001), visual search (Cormack, Aarsland, Ballard, & Tovée, 2004), and visuoconstruction (Aarsland et al., 2003). DLB patients with severe visuospatial deficits are more likely than those with mild deficits to develop visual hallucinations during the course of disease, and the severity of visuospatial impairment may predict the rate of subsequent global cognitive decline (Hamilton et al., 2008).

Consistent with disproportionally severe deficits in visuospatial processes, PET studies have shown hypometabolism, and single-photon emission computed tomography (SPECT) studies have shown hypoperfusion, within the primary visual cortex and visual association cortex in DLB but not in AD (Ishii et al., 1999; Minoshima et al., 2001). These studies found greater deficits in metabolism and blood flow to lateral occipitotemporal areas than medial and ventral areas. Other studies have found hypometabolism within posterior association areas that include parieto-occipital (Colloby et al., 2002; Ishii et al., 2007) and temporoparietal cortex (Ishii et al., 2007). An fMRI
study found reduced BOLD signal in DLB compared to AD within the lateral occipitotemporal cortex during a visual motion detection task, and within the ventral occipito-temporal cortex during a face recognition task (Sauer, fffytche, Ballard, Brown, & Howard, 2006).

Pathological studies have found white matter spongiform change with coexisting gliosis (Higuchi et al., 2000) and Lewy bodies (Gómez-Tortosa et al., 1999) within the occipital cortex of DLB patients. These neuropathological findings may help explain the visuospatial dysfunction observed in DLB. However, the pattern of neuropathology typically found in DLB brains is more frequently located within limbic structures, particularly the anterior cingulate cortex; entorhinal cortex; amygdala; and frontal, parietal, and temporal association areas (Kövari, Horvath, & Bouras, 2009). Lewy body pathology itself does not consistently correlate with cognitive dysfunction, suggesting that other pathophysiological events not necessarily related to Lewy bodies may be responsible for the cognitive deterioration associated with DLB. Some investigators maintain that synapse loss occurs even in the absence of Lewy bodies and shows more robust correlations with clinical symptoms (Duda, 2004). This may account for the apparent lack of occipital Lewy bodies in a substantial portion of DLB patients with visuospatial impairment. An additional complication of correlating neuropathological measures with cognitive symptoms is that Lewy bodies may be present at lower levels in the most advanced stages of the disease due to widespread neuronal loss. Thus, there may be a curvilinear relationship between the degree of Lewy body pathology and the severity of the disease with low levels in the beginning stages, highest levels during the middle stage when Lewy bodies are present but neuronal loss is not widespread, and low levels again during the most advanced stage with extensive neuronal loss.

The prominent visuospatial deficit and visual hallucinations associated with DLB could be related to neurotransmitter dysfunction (Lippa, Smith, & Perry, 1999). Among the brain regions particularly affected by Lewy body pathology are forebrain areas that make up the cholinergic diffuse activating system, specifically the nucleus basalis of Meynert and the interstitial nucleus of the diagonal band (Lippa et al., 1999). Although these changes are analogous to those seen in AD, there is much more extensive pathological involvement and neuronal loss of the nucleus basalis in DLB than in AD. Choline acetyltransferase, the enzyme responsible for the synthesis of the neurotransmitter acetylcholine, is manufactured within the cell bodies of the nucleus basalis and transported to axonal terminals diffusely spread throughout the neocortex. Levels of this enzyme represent a stable marker of acetylcholine activity at the synapse and have been found to be depleted even during the early stages of DLB and to a much greater degree than in AD (Lippa et al., 1999). Although AD patients exhibit a compensatory upregulation of cholinergic activity within limbic and neocortical regions after damage to the basal forebrain, DLB patients show a lack of compensatory response.

Similar to clinical symptomatology, neurotransmitter changes in DLB do not necessarily correlate with neuropathological measures of Lewy body disease (Perry et al., 1995). In contrast, measures of neurotransmitter dysfunction do correlate with cognitive and other clinical symptoms in DLB. For instance, DLB patients with visual hallucinations show greater cholinergic deficits than those without hallucinations within the temporal cortex with a known role in visual recognition (e.g., Brodman area 36; Ballard et al., 2000). Cholinergic deficits are found throughout the entire neocortex in DLB to a greater extent than in AD. DLB and AD patients both show deficits in expression of the M1 muscarinic receptor in the hippocampus, but DLB
patients exhibit a relative preservation of neocortical M1 receptor expression while AD patients do not. This may account for the greater clinical response to cholinesterase inhibitor therapy observed in DLB patients (McKeith et al., 2000). Additional cholinergic deficits observed in DLB include decreased expression of high-affinity nicotinic receptors within the substantia nigra and temporal cortex (Duda, 2004). Low-affinity nicotinic receptors are also underexpressed in DLB. Underexpression of low-affinity nicotinic receptors within temporal areas important for visual processing (i.e., Brodman areas 20 and 36) and high-affinity receptors within occipital areas has been associated with visual hallucinations in DLB (Court et al., 2001; O’Brien et al., 2008).

Executive Functions

In addition to prominent visuospatial deficits, DLB patients exhibit disproportionate executive dysfunction relative to AD patients. These deficits are evident on tests of attention (Hansen et al., 1990), initiation and perseveration (Aarsland et al., 2003), verbal fluency (Galasko, Katzman, Salmon, & Hansen, 1996), and abstract reasoning (Shimomura et al., 1998). Other attentional and executive abilities disproportionately impaired in DLB relative to AD include visual attention (Sahgal et al., 1992) and spatial working memory (Sahgal, McKeith, Galloway, Tasker, & Steckler, 1995). These findings are consistent with the presence of Lewy bodies within the frontal lobes of DLB patients and with evidence of cholinergic dysfunction, hypometabolism, and hypoperfusion of the frontal cortex that is more prominent in DLB than in AD (Fong, Inouye, Dai, Press, & Alsop, 2011). Cholinergic nicotinic receptor activity is associated with the progression of executive dysfunction in both AD and DLB (Colloby et al., 2010).

Memory

One robust finding distinguishing DLB from AD is the relative preservation of MTL structures such as the hippocampus, entorhinal cortex, and parahippocampal gyrus in DLB compared to AD (Sabattoli et al., 2008; Watson et al., 2009). This distinction is consistent with milder memory impairment in DLB than in AD, despite similar levels of global cognitive dysfunction (Hamilton et al., 2004). The mild memory impairment of DLB patients is often characterized by difficulty learning new information, a relatively preserved ability to retain what is learned, and enhanced performance with cuing or recognition testing compared to free recall (Salmon et al., 1996). This contrasts with the memory impairment of AD, which is characterized by impaired learning, poor retention over time, and little or no enhancement of performance with recognition testing (Calderon et al., 2001). The relatively good retention and improvement in performance when retrieval demands are reduced with recognition testing suggests that a deficit in retrieval plays a greater role in the memory impairment of DLB than AD. This is likely because subcortical and/or frontal lobe dysfunction contributes more to the memory deficit in DLB than in AD. In addition, there is a different pattern of atrophy and cholinergic receptor expression in the hippocampus in DLB and AD (Watson et al., 2009). Pathological findings indicate that MTL atrophy in DLB is associated with senile plaques and neurofibrillary tangles, but not Lewy body pathology (Burton et al., 2009). Thus, the relative preservation of memory in DLB may be related to the relative lack of concomitant AD pathology.
FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) is a clinicopathological condition characterized by deterioration of personality and cognition associated with prominent frontal and temporal lobar atrophy. Although FTD is relatively uncommon in older adults, its prevalence rivals that of AD in individuals younger than 65 years (Ratnavalli, Brayne, Dawson, & Hodges, 2002). Frontotemporal lobar degenerative disorders manifest as three separate clinical syndromes that may be distinguished by early prominent symptoms: (a) behavioral variant FTD (bvFTD) characterized by early change in personality, behavior, and cognition associated with frontal lobe atrophy; (b) semantic dementia (SD) characterized by early progressive loss of word meanings associated with anterior temporal degeneration; and (c) progressive nonfluent aphasia (PNFA) characterized by an early progressive anomic aphasia associated with deterioration of perisylvian cortical areas (Snowden, Neary, & Mann, 2007). Although these specific clinical syndromes can be distinguished early in the course of the disease, more advanced presentations often involve more generalized cognitive decline and combinations of features. Neuropathological findings in FTD include predominantly tau-positive (FTD-TAU) inclusions in PNFA, ubiquitinated TAR DNA-binding protein 43 (TDP-43)-positive (FTD-TDP) inclusion bodies in SD, and an equal proportion of both pathologies in bvFTD (Hodges et al., 2004; Seelaar et al., 2010; Shi et al., 2005; Snowden et al., 2007). The minority of remaining cases contain either RNA-binding protein fused in sarcoma (FUS)-positive bodies, other FUS- and TDP-negative but ubiquitin-positive bodies, or no distinctive histopathology (Seelaar et al., 2010).

The clinical and neuropathological features of FTD overlap with several other distinct conditions, including corticobasal degeneration, PSP, and amyotrophic lateral sclerosis (Josephs, 2008). Gene mutations identified in familial variants of FTD account for between 5% and 11% of cases and include microtubule-associated protein tau (MAPT) associated with FTD-TAU and progranulin (PGRN) associated with FTD-TDP (Rohrer et al., 2009). In a major recent discovery, the expansion of a non-coding GGGGCC sequence linked to chromosome 9p21 was found to be the most common genetic abnormality in familial FTD, accounting for 11.7% of cases in one sample (DeJesus-Hernandez et al., 2011).

Behavioral Variant

bvFTD begins with an insidiously progressive alteration in personality and behavior that may include inappropriate social conduct, inertia and apathy, disinhibition, perseverative behavior, loss of insight, hyperorality, or decreased speech output (Grossman, 2002). These alterations in behavior and personality have been linked to atrophy and neuropathological changes within the rostral limbic system, including the anterior cingulate, anterior insular, amygdala, orbitofrontal, ventrolateral frontal, ventromedial frontal, and ventral neo striatal areas (Snowden et al., 2007). These regions are thought to underlie processing and output related to socially appropriate behavior, which may include evaluating motivational and emotional content of internal and external stimuli, decision making, and error detection (Boccardi et al., 2005; Rolls, 2000). Recent histopathological and neuroimaging (e.g., MRI and SPECT) studies have specifically implicated the selective vulnerability of bipolar von Economo neurons located in layer V of the anterior cingulate, orbitofrontal, medial frontal, and insular areas in the early pathogenesis of bvFTD (Seeley, 2008). These neurons play a critical role in the integration of visceral-autonomic inputs that guide social-emotional behavior (Craig, 2002). Early disruption of the pathways involving these neurons may contribute to the initial behavioral symptoms observed in bvFTD.
neurons within the rostral limbic system is consistent with the initial behavioral manifestations of bvFTD.

There may also be cognitive deficits in bvFTD that include alterations in judgment, problem solving, concept formation, and executive functions, with a relative sparing of visuospatial and memory abilities (Libon et al., 2009). Although aspects of the personality changes found in bvFTD differ from those typically found in other neurodegenerative conditions, many of these features overlap significantly with behavioral changes associated with AD (Varma et al., 1999). Many of the cognitive deficits found in these patients also overlap with those found in AD, particularly with regard to language impairment and executive dysfunction. Comparison with other forms of dementia is necessary to establish the cognitive profile specific to FTD; however, these studies are challenged by a number of methodological difficulties (Wittenberg et al., 2008). First, studies must match FTD patients to patients with other forms of dementia, particularly AD, in terms of dementia severity in order to compare their pattern of neuropsychological test performance. Second, many studies label participants generically as FTD without specifying participants by one of the three initial clinical presentations (i.e., bvFTD, SD, and PNFA). Finally, studies require clinico-neuropathological confirmation of bvFTD to assure the diagnosis and the lack of AD pathology that could contaminate the results of cognitive analyses.

Although these limitations have led to mixed findings concerning the cognitive signature of bvFTD, some general statements can be made regarding the pattern of test performance between FTD patients and those with AD. For example, FTD patients exhibit more severe deficits in executive functions than in other cognitive abilities, whereas AD patients have executive dysfunction that is proportional to their deficits in language and visuospatial abilities and less prominent than their episodic memory deficit (Förstl et al., 1996; Starkstein et al., 1994). Patients with mild-to-moderate FTD display greater impairment on word generation tasks (i.e., letter and category fluency tasks) but less impairment on tests of memory and visuospatial abilities compared to patients with AD (Rascovsky et al., 2002). These findings are consistent with greater frontal and anterior and lateral temporal lobe involvement in FTD than in AD, with relative sparing of medial temporal and parietal association areas only in FTD (Grossman et al., 2007; Libon et al., 2007). It is interesting to note that in terms of verbal fluency, FTD patients were equally impaired on all word generation tasks while AD patients showed greater impairment on semantic fluency than phonemic fluency tasks. This suggests that FTD patients’ deficits were primarily driven by poor effortful retrieval and diminished active strategic search that may depend on frontal lobe function, whereas the impairment of patients with AD was at least partially driven by semantic deficits related to temporal lobe neocortical dysfunction. Importantly, FTD patients presenting with PNFA or SD show greater impairment on semantic fluency than letter fluency tasks, similar to AD patients, presumably due to temporal lobe neocortex damage in those FTD subtypes. Thus, greater impairment (relative to normal controls) of letter fluency than semantic fluency may represent a pattern of cognitive impairment that is somewhat specific to bvFTD (Mesulam, 1982).

Some studies have failed to find significant differences in visuospatial-constructional abilities between bvFTD and AD patients when using the Rey–Osterrieth Complex Figure copying task (Lindau, Almkvist, Johansson, & Wahlund, 1998). However, this task is known to not only require intact visuospatial abilities, but also may be influenced by attentional and strategic-organizational requirements dependent upon the frontal lobes (Varma et al., 1999). In support of this distinction, a
A recent neuroimaging study found that poor performance on this complex figure task was correlated with right parietal cortex atrophy in AD and right prefrontal cortex atrophy in bvFTD (Possin, Laluz, Alcantar, Miller, & Kramer, 2011).

As the studies reviewed in the previous pages suggest, the cognitive deficits associated with bvFTD are related to neuropathological changes within frontal and temporal cortices. Histopathological studies of FTD have revealed loss of projecting pyramidal cells with glutamatergic activity and local-circuit inhibitory neurons within the upper cortical layers of the frontal cortex (Ferrer, 1999). Other findings indicate loss of postsynaptic sites within the remaining neurons of these upper cortical layers (Kersaitis, Halliday, & Kril, 2004). Cognitive changes typically follow changes in personality and behavior in bvFTD, suggesting that the temporal manifestation of cognitive dysfunction may be related to the progression of neuropathology. Studies examining the time course of frontotemporal neuropathology suggest that there is early mild atrophy of orbital and superior medial frontal cortices and hippocampus, followed by anterior frontal, temporal, and basal ganglia atrophy, and finally involvement of all remaining frontotemporal areas (Broe et al., 2003). Although it remains unclear what specific brain regions are responsible for various aspects of cognitive impairment in bvFTD, more severe and widespread atrophy may correlate with the extent of cognitive symptoms.

**Progressive Nonfluent Aphasia**

Patients presenting with a protracted period of aphasia often lasting years prior to the onset of more generalized cognitive decline represent a minority of FTD patients. These individuals exhibit two to three forms of aphasia, including nonfluent, semantic, and logopenic. Neuroimaging and postmortem autopsy studies have indicated that patients with FTD-PNFA show greater temporal lobe than frontal lobe pathology.

PNFA (also termed primary progressive aphasia) is characterized by hesitant speech production (i.e., apraxia of speech), agrammatism, deficits in processing syntactically complex sentences, anomia, and enhanced commission of phonemic paraphasic errors with relative preservation of word comprehension (Grossman, 2002). Measures of grammatical impairment, such as sentence comprehension tasks (Hodges & Patterson, 1996), are particularly sensitive to PNFA. Grammatical impairment may be particularly important in the language deficits observed in these patients, as they show greater deficits on sentence-picture matching tasks requiring an appreciation of grammatical relationships than word–picture matching and word-reading ability (Hodges & Patterson, 1996).

Functional neuroimaging studies using PET, SPECT, and fMRI suggest decreased cortical activity within the inferior and dorsolateral prefrontal cortex and the superior temporal cortex, possibly extending into the inferior parietal cortex, of the left hemisphere (Grossman, 2010). Some studies further indicate that during grammatical comprehension tasks, particularly for complex sentences, these patients exhibit reduced cortical activity that is poorly correlated with task performance (Cooke et al., 2003; Grossman et al., 1998). These findings correspond well with findings from structural neuroimaging studies. The earliest areas to be affected structurally are the anterior perisylvian regions, including the inferior, opercular, and insular areas of the frontal lobe (Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004). With disease progression, atrophy spreads to the dorsolateral prefrontal cortex, orbital and anterior cingulate regions, and superior temporal cortex (Grossman, 2010).
Semantic Dementia

The SD subtype of FTD presents with a “fluent” aphasia characterized by empty speech, prominent anomia, circumlocution, frequent semantic paraphasic errors, and difficulty understanding the meaning of words with relatively preserved syntax and phonology (Hodges, Patterson, Oxbury, & Funnell, 1992). This pattern of language deficits is thought to be due to deterioration of representational or semantic knowledge. In support of this hypothesis, studies have found that when a particular concept becomes degraded in SD, it cannot be accessed by any modality (e.g., auditory recognition, confrontation naming, word–picture matching; Hodges, Patterson, et al., 1992). Furthermore, the loss of semantic knowledge occurs from the “bottom-up” direction in that the subordinate features of a concept (e.g., knowing that a horse is domestic) are lost before the superordinate features (e.g., knowing that a horse is an animal). Most other cognitive abilities remain relatively intact during the early stages, including episodic memory, nonverbal problem solving, working memory, and visuospatial abilities (Snowden, 1999).

This circumscribed semantic deficit is consistent with findings from neuroimaging studies that indicate prominent and relatively circumscribed left temporal lobe atrophy in patients with SD. Specifically, the left anterior temporal lobe is heavily affected with relative preservation of MTL structures (Hodges & Patterson, 1996). Functional neuroimaging with PET or SPECT reveals cortical hypometabolism within the left temporal lobe extending into the inferior frontal lobe (Grossman, 2002). Some studies have also found decreased recruitment of the left posterior inferior temporal cortex during a semantic decision task (Mummery et al., 1999).

On tests of remote semantic memory (e.g., the famous faces test) patients with SD show a pattern of memory impairment characterized by severe retrograde amnesia with memories from the recent past better retained than memories from the distant past (Graham, Becker, & Hodges, 1997). This is the opposite pattern of that seen in AD where the remote memory deficit shows a temporal gradient with memories from the more distant past better retained than those from the recent past (Beatty, Salmon, Butters, Heindel, & Granholm, 1988). This double dissociation is thought to be indicative of the distinction between the hippocampally based memory impairment seen in AD and the cortically based impairment seen in SD (Hodges & Graham, 1998). While AD is associated with prominent disease within MTL structures (e.g., the hippocampus), SD is associated with prominent disease within the left perisylvian cortex (Hodges & Patterson, 1996). This distinction is evident early in the course of these conditions, but may become less salient as patients with AD experience a gradual shift from hippocampally based impairment to cortically based impairment (Masliah & Salmon, 1999).

VASCULAR DEMENTIA

VaD refers to a cumulative decline in cognitive functioning secondary to parenchymal damage of vascular origin that is sufficient to cause impairment in activities of daily living. There are a number of difficulties in the definition of VaD due to the heterogeneity of its underlying etiology and clinical presentation. There is a wide range of vascular etiologies that may lead to the brain injury and resulting cognitive impairment responsible for VaD. These include but are not limited to multiple large infarctions, strategically placed infarctions, multiple small ischemic injuries, hemorrhagic lesions, and degenerative changes secondary to ischemia (e.g., hippocampal sclerosis or gliosis; Ince, 2005). Due to the heterogeneous nature of these different
forms of neuropathology, there is no accepted neuropathological scheme for quantifying cerebrovascular disease as a whole with a “vascular pathology score” analogous to the Braak and Braak score for AD pathology (Braak, Braak, & Bohl, 1993; Jellinger, 2007b). The clinical presentation of VaD is also quite variable because the nature of a given patient’s cognitive impairment will be determined by such a broad range of etiologies. Consequently, there is no singular or specific neuropsychological profile for VaD in general. For example, even within the subgroup of patients with VaD due to multiple large infarctions, the clinical presentation may vary dramatically according to the location of the infarctions. The necessity of memory impairment for DSM-IV-TR criteria for dementia is particularly problematic for VaD since patients may have profound deficits in multiple cognitive domains without memory impairment if their lesions are limited to cortical regions that are not critical for memory function (Wetterling, Kanitz, & Borgis, 1996).

As a result of these and other nosological difficulties, there is no single set of criteria for the clinical diagnosis of VaD that is generally accepted; consequently, prevalence estimates and other generalizations regarding the condition remain controversial (Chui, 2006; Jellinger, 2007b). Nevertheless, various attempts have been made to break the diagnosis into several subcategories, some of which may be more specifically characterized neuropsychologically. These conditions generally fall into at least three large categories: multi-infarct dementia (MID) associated with multiple large cortical infarctions (usually affecting 10 mL or more of brain tissue), dementia due to a single strategically placed infarction, and subcortical ischemic vascular dementia due to subcortical small-vessel disease that results from multiple lacunar strokes, leukoaraiosis (Binswanger’s disease), or diffuse white matter pathology (Kalaria et al., 2004).

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

A recent statement from the American Heart Association and the American Stroke Association made an attempt to redefine VaD in light of the many problems with current conceptualizations (Gorelick et al., 2011). The term vascular cognitive impairment was used to indicate any cognitive impairment thought to be due to any form of vascular disease. The use of this broader term is favored because it improves the recognition of individuals with cognitive impairment that has not yet reached the severity of dementia, which may allow for earlier identification and treatment of high-risk patients (Hachinski, 1992). Vascular cognitive impairment is then broken down into VaD and vascular mild cognitive impairment,
which anticipates the likelihood that the DSM-5 will break dementia into major neurocognitive disorder and minor neurocognitive disorder (www.dsm5.org). Memory is no longer required for the diagnosis of VaD and the emphasis is placed on executive dysfunction. These criteria also de-emphasize the presence of neurological signs, biomarkers, and stepwise decline since research has consistently failed to demonstrate their sensitivity to VaD (Erkinjuntti & Gauthier, 2002). Imaging remains an important component of the diagnosis because it is required to show evidence of cerebrovascular disease unless there is a history of clinical stroke. There is also increased recognition of the substantial overlap between AD and ischemia (Schneider, 2009), which cannot be readily disentangled by current imaging or biomarker technologies (Chui et al., 2006; Jellinger, 2007a). These new criteria represent a major advancement in the diagnosis of VaD, and the importance of neuropsychological testing is featured prominently. This makes cognitive function in VaD and vascular mild cognitive impairment an attractive area for future research in neuropsychology.

The most likely VaD etiologies to produce a cortical dementia that requires memory impairment are MID and a strategic infarct. MID usually occurs due to cortical lesions arising from occlusions of the main branches of the anterior, middle, or posterior cerebral arteries. Depending on the specific site and size of the cortical lesions, MID is characterized by memory impairment, aphasia, agnosia, and/or apraxia. The cognitive deficits of MID usually have a sudden onset and progress in a stepwise fashion as successive occlusions occur. A single strategically placed infarct can also lead to a cortical dementia syndrome if it involves brain areas important for memory, language, or visuospatial abilities. For example, an anterior cerebral or middle cerebral artery infarct that affects the angular gyrus can cause poor memory, alexia with agraphia, constructional apraxia, and anomia. Studies have shown that strokes within the posterior cerebral artery territory are particularly likely to result in dementia, including lesions affecting the dorsal paramedian areas of the thalamus, which can cause a diencephalic amnestic disorder, and lesions involving mesial temporal areas causing AD-like amnesia (Castaigne et al., 1981; Glees & Griffith, 1952). Ischemic lesions within the orbitofrontal, medial frontal, and cingulate areas supplied by the anterior cerebral artery, and caudate nucleus lesions involving the lateral lenticulostriatal arteries of the middle cerebral artery, also cause behavioral disturbances resulting in dementia (Mendez, Adams, & Lewandowski, 1989; Zekry et al., 2003). Other causes of VaD, such as a subarachnoid hemorrhage, can cause memory impairment, frontal lobe dysfunction, and language deficits that are usually associated with the cortical dementia syndrome (Jellinger, 2007b). It is interesting to consider what brain regions may emerge as “strategic infarct zones” with the new VaD criteria that no longer require memory impairment for the diagnosis. This subtype of VaD may be more common under the new criteria and is likely to involve a much greater variety of brain areas because the diagnosis of VaD simply requires impairment in two or more cognitive domains with substantial decline in activities of daily living (Gorelick et al., 2011).

A particularly important area of research in the neuropsychology of VaD involves the cognitive characterization of subcortical ischemic small vessel disease (Pantoni, 2010). This VaD subtype, formerly referred to as Binswanger’s disease (Libon, Price, Davis Garrett, & Giovannetti, 2004), is characterized by extensive subcortical white matter lesions with no cortical infarcts observed on MRI. The relatively circumscribed damage to the white matter suggests that there may be an identifiable neuropsychological syndrome or profile associated with the disease, which would
make this form of VaD more readily definable by operationalized research criteria. One challenge to this field is the high rates of subcortical white matter disease in VaD, AD, mixed dementia, and normal adults (O’Brien et al., 2002). Studies comparing the neuropsychological deficits associated with this subcortical form of VaD and AD largely show that patients with VaD are more impaired than those with AD on tests of executive functions, whereas patients with AD are more impaired than those with VaD on tests of episodic memory (particularly delayed recall). In addition, these studies suggest that the executive dysfunction associated with VaD is its most prominent deficit, perhaps because white matter pathology interrupts fronto-subcortical circuits that mediate this aspect of cognition. One study showed that VaD patients with a significant volume of white matter abnormality on imaging exhibited a profile of greater executive dysfunction and visuoconstructional impairment than impairment of memory and language abilities (Mathias & Burke, 2009; Price, Jefferson, Merino, Heilman, & Libon, 2005). These findings have been generally confirmed in a recent meta-analysis that included studies that used neuropsychological test performance to differentiate between VaD and AD (Mathias & Burke, 2009). Although this analysis showed that cognitive measures were limited in their ability to discriminate between the two disorders, patients with VaD were more impaired than patients with AD on tests that required recognition of emotions in pictured faces, whereas patients with AD were more impaired than those with VaD on tests of episodic memory that required delayed recall.

Neuropsychological studies provide consistent evidence for distinct cognitive profiles in VaD and AD, yet almost all of these studies employed clinically diagnosed patients without autopsy confirmation of diagnosis. This may have led to some degree of misclassification of patients across groups because AD and VaD are quite heterogeneous and can overlap in their clinical presentations. To avoid this potential confound, a recent study compared the profiles of neuropsychological deficits exhibited by patients with autopsy-confirmed VaD (primarily subcortical vascular pathology) or AD (Reed et al., 2007). Consistent with previous studies of clinically diagnosed patients, patients with AD had a deficit in episodic memory (both verbal and nonverbal memory) that was significantly greater than their executive function deficit. In contrast, patients with VaD had a deficit in executive functions that was greater than their deficit in verbal (but not nonverbal) episodic memory, but this difference was not significant. To further explore these differences, an analysis of individual patient profiles was carried out. This analysis showed that 71% of AD patients exhibited a profile with memory impairment more prominent than executive dysfunction, whereas only 45% of patients with VaD exhibited a profile with more prominent executive dysfunction than memory impairment. Interestingly, relatively severe cerebrovascular disease at autopsy was often not associated with clinically significant cognitive decline. When the profile analysis was restricted to those patients who exhibited significant cognitive impairment at their clinical assessment, the distinction between VaD and AD patients was more pronounced with 79% of AD patients exhibiting a low memory profile (5% with a low executive profile) and 67% of VaD patients exhibiting a low executive profile (0% with a low memory profile). The results of this study suggest that relatively distinct cognitive deficit profiles might be clinically useful in differentiating between VaD and AD, but additional research with autopsy diagnosed patients is needed to further characterize the deficit profile that will best differentiate between these disorders.

The distinction between AD and VaD on the basis of dysexecutive versus memory impairment is likely due to the more prominent involvement of subcortical
dysfunction in VaD than in AD (Pantoni, 2010). Thus, VaD patients with subcortical vascular disease may be more readily characterized than other forms of VaD as neuropsychologically distinct from AD. It should be noted, however, that a dysexecutive syndrome can also occur as the result of cortical pathology that directly affects the frontal cortex (e.g., as in FTD).

Patients with VaD due to MID or strategic infarcts may mimic a variety of cortical syndromes including frontal lobe associated behavioral and cognitive deficits of bvFTD, prominent episodic memory deficit of AD, or aphasia associated with PNFA or SD. This is due to the fact that cortical infarction may occur in nearly any cortical region and result in the total ablation of the associated cognitive ability. For example, all forms of aphasia may result from strokes within a variety of frontal and temporal regions perfused by the middle cerebral artery (e.g., Broca’s area, Wernicke’s area). Behavioral syndromes found in bvFTD and AD (e.g., disinhibition, inertia) may result from orbitofrontal or medial frontal lobe infarction. Forms of visual agnosia (e.g., Balint’s syndrome, object recognition deficits) found in PCA (i.e., visual variant of AD) may result from posterior cerebral artery infarction. There are certain cortical syndromes, however, that are relatively specific to vascular disease. For example, left hemispatial neglect may result from right middle cerebral artery infarction, but is rarely caused by a nonvascular neurodegenerative disease.

Heterogeneity of presentation is a feature of VaD that is difficult to quantify or apply to the “average” case, or to incorporate into research criteria. However, it is frequently helpful to note the “spotty” presentation of cognitive deficits when making a clinical differential diagnosis of VaD because that characteristic differs from the fairly typical presentation and course of most other cortical neurodegenerative diseases. One promising approach involves the use of intra- and inter-test variability measures to quantify the degree of performance variability within and across test domains (Crawford, Garthwaite, Howell, & Venneri, 2003; Schretlen, Munro, Anthony, & Pearlson, 2003). Measurement of variability in test performance may quantify the “spotty” nature of cognitive deficits that is observed in some patients with VaD, but more research is needed before this approach becomes clinically useful.

SUMMARY

The dementias are a clinically heterogeneous group of syndromes whose variations stem from their differences on a neuropathological level. That is, the etiological and neuropathological differences between such neurodegenerative diseases correspond to the relatively distinct neurocognitive profiles of each presentation. This is most obvious when comparing neurodegenerative diseases that primarily involve the cerebral cortex versus those that primarily involve subcortical regions. Although this distinction is not pure (i.e., pathological changes are not limited to either cortical or subcortical regions), the cortical–subcortical dementia distinction serves as a heuristically useful model for describing the pattern of neuropsychological deficits that are observed in these patient groups. Knowledge of the functional link between neuroanatomy and neurophysiology of neurodegenerative processes and neuropsychological outcomes is critical for clinical practice. By understanding this pathology–functional relationship, clinical review and objective assessment can make precise judgments about the etiology and, thus, type of neurodegenerative process.
# TABLE 1.1 Cortical Dementias: Characteristics of Disease Onset, Course, Neurocognition, Neuroimaging, and Neuropathology

<table>
<thead>
<tr>
<th>ONSET AND COURSE</th>
<th>NEUROCOGNITION</th>
<th>NEUROIMAGING</th>
<th>NEUROPATHOLOGY</th>
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<tbody>
<tr>
<td><strong>Alzheimer’s Dementia</strong></td>
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<tr>
<td>Insidious onset with steady decline. Cognitive dysfunction precedes changes in personality and motor function.</td>
<td>• Attention—Basic attention may be preserved early, with deficits in complex attention and working memory.</td>
<td>• Hippocampal atrophy on MRI.</td>
<td>• Amyloid plaques</td>
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<td></td>
<td>• Memory—Rapid forgetting of episodic memories. Minimal improvement in structured format.</td>
<td>• Amyloid positive on PET-Pittsburgh compound B (PiB)</td>
<td>• Neurofibrillary tangles</td>
</tr>
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<td></td>
<td>• Executive Function—Mild deficits early in disease course.</td>
<td></td>
<td>• Cortical and hippocampal atrophy</td>
</tr>
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<td></td>
<td>• Language—Early deficits in semantic fluency progress to anomia and agnosia.</td>
<td></td>
<td>• Cerebral amyloid angiopathy</td>
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<td></td>
<td>• Visuospatial—Deficits emerge during moderate stages of the disease.</td>
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<td><strong>Dementia With Lewy Bodies</strong></td>
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<td>Cognitive deficit occurs with or before motor signs (no or mild tremor). Vivid visual hallucinations, REM behavior disorder, and fluctuating cognition may be present.</td>
<td>• Memory—Mild retrieval-based memory deficit.</td>
<td>• Reduced posterior metabolism on PET.</td>
<td>• Cortical and subcortical Lewy bodies</td>
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<tr>
<td></td>
<td>• Visuospatial function—Prominent early deficits disproportionate to memory deficits.</td>
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<tr>
<td></td>
<td>• Executive function—Prominent early deficits disproportionate to memory deficits.</td>
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<tr>
<td></td>
<td>• Reduced posterior metabolism on PET.</td>
<td>• Cortical atrophy.</td>
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<td></td>
<td>• Cortical and subcortical Lewy bodies</td>
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<tr>
<td><strong>Frontotemporal Dementia</strong></td>
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<tr>
<td>Early age of onset. Insidious onset with steady decline. Preservation of episodic memory.</td>
<td>• Behavioral variant (BV)—Early prominent personality changes prior to cognitive decline. Reduced verbal output and/or executive dysfunction may be present.</td>
<td>• BV—Atrophy of frontal regions.</td>
<td>• Atrophy of frontotemporal regions</td>
</tr>
<tr>
<td></td>
<td>• Progressive nonfluent aphasia (PNFA)—Early prominent nonfluent aphasia with intact comprehension.</td>
<td>• PNFA—Atrophy of perisylvian regions.</td>
<td>• FTD-TAU bodies or …</td>
</tr>
<tr>
<td></td>
<td>• Semantic dementia (SD)—Early prominent semantic memory loss with fluent speech.</td>
<td>• SD—Atrophy of anterior temporal regions.</td>
<td>• FTD-TDP bodies or …</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Atrophy of frontotemporal regions</td>
<td>• FUS bodies</td>
</tr>
<tr>
<td></td>
<td>• BV—Atrophy of frontal regions.</td>
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<td></td>
<td>• PNFA—Atrophy of perisylvian regions.</td>
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<td>• SD—Atrophy of anterior temporal regions.</td>
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<td></td>
<td>• Atrophy of frontotemporal regions</td>
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<td>• FTD-TAU bodies or …</td>
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<td></td>
<td>• FTD-TDP bodies or …</td>
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<tr>
<td><strong>Vascular Dementia</strong></td>
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<tr>
<td>Abrupt onset with stepwise decline. May show striking contrast between areas of preservation versus impairment.</td>
<td>• Memory—Mild retrieval-based memory impairment.</td>
<td>• Severe subcortical white matter disease or …</td>
<td>• Infarctions</td>
</tr>
<tr>
<td></td>
<td>• Executive function—Impairment is equal to or greater than memory deficits.</td>
<td>• Multiple large infarcts or …</td>
<td>• Hemorrhages</td>
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<td></td>
<td>• Increased variability across cognitive domains.</td>
<td>• Strategic infarct on MRI</td>
<td>• White and gray matter rarefaction</td>
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<td></td>
<td></td>
<td></td>
<td>• Atherosclerosis</td>
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<td></td>
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<td>• Arteriosclerosis</td>
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</table>

FTD-TAU, frontotemporal dementia predominantly tau-positive; FTD-TDP, ubiquitinated TAU DNA-binding protein 43 (TDP-43)-positive; PET, positron emission tomography; REM, rapid eye movement.
REFERENCES


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