EXPERT REVIEWS

Distinguishing Alzheimer's disease from other major forms of dementia

Expert Rev. Neurother. 11(11), 1579–1591 (2011)

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Alzheimer's disease (AD) is the most common and most studied cause of dementia. Significant advances have been made since the first set of clinical criteria for AD were put forth in 1984 that are now captured in the new criteria for AD published in 2011. Key features include recognition of a broad AD spectrum (from preclinical to mild cognitive impairment to AD dementia) and requirement of AD biomarkers for diagnosis. Correctly diagnosing dementia type is increasingly important in an era when potential disease-modifying agents are soon to be marketed. The typical AD dementia syndrome has at its core, an amnestic syndrome of the hippocampal type, followed by associated deficits in word-finding, spatial cognition, executive functions and neuropsychiatric changes. Atypical presentations of AD have also been identified that are presumed to have a different disease course. It can be difficult to distinguish between the various dementia syndromes given the overlap in many common clinical features across the dementias. The clinical difficulty in diagnosis may reflect the underlying pathology, as AD often co-occurs with other pathologies at autopsy, such as cerebrovascular disease or Lewy bodies. Neuropsychological evaluation has provided clinicians and researchers with profiles of cognitive strengths and weaknesses that help to define the dementias. There is yet no single behavioral marker that can reliably discriminate AD from the other dementias. The combined investigation of cognitive and neurobehavioral symptoms coupled with imaging markers could provide a more accurate approach for differentiating between AD and other major dementia syndromes in the future.

Keywords: Alzheimer's disease • cognition • dementia • depression • differential diagnosis • frontotemporal dementia • Lewy body • vascular

 10.1586/ERN.11.155 ISSN 1473-7175

Financial & competing interests disclosure
Editor
Elisa Manzotti, *Editorial Director, Future Science Group, London, UK*
Disclosure: *Elisa Manzotti has disclosed no relevant financial relationships.*
CME Author
Laurie Barclay, MD, *Freelance writer and reviewer, Medscape, LLC*
Disclosure: *Laurie Barclay, MD, has disclosed no relevant financial relationships.*
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Disclosure: *Stella Karantzoulis has received a grant from the National Institute on Aging (P30 AG008051-21) for this report. She has disclosed no other relevant financial relationships.*
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Disclosure: *James E Galvin has received a a grant from the National Institute on Aging (P30 AG008051-21) for this report. He has disclosed no other relevant financial relationships.*

Distinguishing AD dementia from other major forms of dementia

Alzheimer's disease (AD) is a degenerative brain disease that usually begins in late life and results in a progressive dementia. AD is characterized pathologically by neuronal atrophy, synapse loss and the abnormal accumulation of amyloid-β protein (Aβ) as senile plaques and hyperphosphorylated tau protein as neurofibrillary tangles. In most cases, neurofibrillary tangles initially involve medial temporal lobe structures (e.g., hippocampus and entorhinal cortex) and then extend to temporal, parietal and frontal lobe association areas as the disease progresses, while Aβ deposition begins in parietal, temporal and frontal association areas [1]. Primary sensory and motor cortices and most subcortical structures are relatively spared until late in the disease process. Degeneration in basal forebrain structures results in a major reduction of cortical, limbic and hippocampal cholinergic projections. The typical dementia syndrome of AD is characterized by prominent episodic memory impairment, with secondary deficits in word-finding skills, spatial cognition and executive functions [2]. These cognitive deficits and the decline in everyday functions that they cause make up the core features of the AD dementia syndrome.

Diagnostic criteria for AD were first published in 1984 [3]. Since that time, a great deal more has been learned about the pathologic events and course of AD that has significantly advanced our view of the disease. New criteria for AD were published in 2011 that reflect these advances [4]. The clinical criteria for the AD dementia syndrome are similar to those outlined 27 years ago and include an insidious onset of months to years (not days to weeks), clear-cut history of progressive cognitive deterioration and associated decline in activities of daily living (usually obtained from an informant and corroborated with neuropsychological testing), and consideration that potential causes other than AD dementia (e.g., delirium, systemic or neurological illness) are not the primary contributing factor(s). Different phenotypic variants of AD dementia are recognized, including the typical amnestic (primary impairments in learning and recall of newly acquired information) and atypical nonamnestic (primary deficits in word-finding, spatial cognition or executive functions) forms [4]. According to the new criteria, a diagnosis of probable AD can be made when the clinical and cognitive criteria described above are met and there is either documented progressive cognitive decline, abnormal biomarker(s) suggestive of AD or evidence of proven AD autosomal dominant genetic mutation (*PSEN1*, *PSEN2* and *APP*). Criteria for a diagnosis of possible AD can be made when there is an atypical course, when the clinical and cognitive criteria are met, but there are no biomarkers to support the diagnosis or when there is evidence of a secondary disorder that can cause dementia. The diagnosis of definite AD can only be made when there is histopathological confirmation from a biopsy or autopsy and the clinical criteria for AD are met.

The idea that AD is preceded by a long period of subtle cognitive decline is also central to the new criteria [5]. Three possible stages of the AD process are formalized: preclinical, mild cognitive impairment (MCI) and AD dementia [6]. The construct of MCI has been extensively discussed in the literature since its conceptualization in the early 1990s. MCI refers to the period in which there is objective evidence of cognitive impairment, often endorsed by an informant; however, the impairment is not sufficient to interfere with daily activities [7]. New clinical criteria for MCI due to AD were also formalized this year that account for the fact that most cases of MCI do progress to clinical AD and that most patients do exhibit at least some interference with daily activities. The preclinical phase of AD is defined primarily by biomarker data, revolutionized by the use of PET imaging and cerebrospinal fluid analyses of Aβ and tau. The preclinical phase is meant to capture the broad spectrum ranging from completely asymptomatic individuals with biomarker evidence of AD pathologic change to individuals exhibiting subtle cognitive decline but who do not yet meet accepted clinical criteria for MCI. The preclinical phase is intended to facilitate the development of more effective treatments that target primary pathological processes at earlier stages of the disease process [5].

Given the well-defined criteria, one might suspect that diagnosis of AD in 2011 is sufficiently advanced so as to eliminate confusion about whether the cause of cognitive decline is due to AD. While there is no question that the progression and clinical course of AD remains better characterized than that of other forms of dementia, the fact remains that patients and research participants alike often present with a variety of cognitive, behavioral, affective and motor disturbances that make diagnosis challenging. There is now sufficient evidence in support of the notion that patients with AD can present with diverse clinical symptoms at the time of the initial evaluation. This can complicate diagnosis and probably

reflects differences in pathology that can only be confirmed at autopsy. Adding to the complexity of diagnostic considerations in AD is that other major dementia syndromes can mimic AD at the time of the initial evaluation.

Owing to the fact that patients rarely (if ever) present with placards clearly stating their diagnosis, in this article, we will review the cognitive and neurobehavioral manifestations of the AD dementia syndrome (in its typical, atypical and mixed forms) and compare and contrast this with the typical, profiles of disorders that are most likely to present as 'AD-mimics'. Although more than 70 known causes of dementia have been recognized, we will limit this article to comparisons between AD, Lewy body dementias (LBD), variants of frontotemporal lobar degeneration and vascular dementia (VaD), as the differential diagnosis of AD and these specific disorders remains a particularly difficult clinical issue. Owing to the complex relationship that exists between depression and dementia, we have also chosen to include comparisons of the cognitive neuropsychological profiles of geriatric depression where relevant. Rather than categorizing by the clinical diagnosis, we focus on cognitive domains and how each disorder impacts on clinical presentation and testing. Table 1 presents the most common dementia syndromes.

Memory

The earliest and most common clinical manifestation of AD is impairment in episodic memory – that is, problems in learning and recalling specific facts from a particular spatiotemporal context. This form of memory is intimately dependent on functioning of medial temporal lobe structures, such as the entorhinal cortex and hippocampus, which are affected early in the disorder by tau-based pathologies [1]. The episodic memory impairment of AD is presumed to be due to a diminished ability to encode new material into long-term memory. This produces a rapid decay of memory traces, affecting both recall and recognition of verbal and visual material [8]. The rate of forgetting in AD is thought to be markedly greater than in other dementias and even more pronounced than in persons with circumscribed amnesia [9,10]. This is also considered to be the reason for the prominent recency effects (i.e., recall of only the last few words presented), frequent intrusion errors (i.e., responding with semantically related words rather than items on the target list under conditions of free recall), and lack of benefit noted with cuing among patients with AD.

In the early stages, there tends to be relative preservation of remote factual information, intact immediate memory (e.g., mental rehearsal of a phone number, encoded in sensory association and prefrontal cortices) and preserved procedural memory (knowing how to perform a task). In the late stage of the AD dementia syndrome, the memory deficit eventuates in a total failure of recall for previously learned information.

Semantic memory is the long-term representation of knowledge about the meaning of words, objects, actions or ideas. Semantic memory is complex and multifaceted and may overlap conceptually and neuroanatomically with episodic memory [11]. A strong consensus holds that AD results in a degradation of core semantic representations [12,13]. As semantic memory is most often assessed with objective measures of naming and category fluency, we will review semantic impairments in AD in the section on language processing.

An atypical variant of AD, known as posterior cortical atrophy (PCA), is characterized neuropsychologically by a disproportionate deficit in visuoperceptual and spatial skills, with milder deficits in memory and executive functions [14]. Pathologically, PCA is a form of AD with greater neurofibrillary tangle burden in the occipital and parietal lobes and lower burden in the hippocampus [15].

Episodic memory impairment is also a key component of the clinical profiles of those patients with MCI who subsequently progress to a diagnosis of AD dementia. Most studies show that the memory profile in this group closely resembles that exhibited by patients with mild AD, with mean episodic memory test scores intermediate between those with mild AD and healthy control subjects [16].

While episodic memory impairment is considered the hallmark clinical feature of AD, the other major dementia syndromes also impact episodic memory performance in manner sufficient to lead to diagnostic challenges. Cognitive deficits in LBD include a mixture of cortical and subcortical symptoms. While many patients with LBD complain of memory decline, the nature of the memory deficit differs from that noted in AD, as it tends to be one of retrieval rather than encoding [17]. Moreover, contrary to the early

Table 1. Major dementia syndromes.

Cause of dementia	Characteristics and clinical and cognitive features
AD	Brain disease that encompasses predementia and dementia phases. Memory changes and AD biomarker evidence required for diagnosis of probable AD. Slow cognitive and functional decline with early loss of awareness. Amnestic and nonamnestic phenotypes
Lewy body dementia	Spectrum of disorders with movement, cognitive, autonomic changes. Includes dementia with Lewy bodies and Parkinson's disease dementia. Early visual hallucinations, muscle rigidity, sleep disturbance. α-synuclein deposits present in neurons
Frontotemporal lobar degeneration	Focal atrophy of frontal and temporal lobes; knife-edge atrophy noted on MRI. Younger onset, changes in personality and behavior, language impairment, strong familial component
VaD	Stepwise progression and focal neurologic signs (also known as multi-infarct dementia or poststroke dementia). Dysexecutive syndrome, slowed processing speed, retrieval difficulties, depression, mild motor signs in subcortical VaD. Symptoms overlap with AD

AD: Alzheimer's disease; VaD: Vascular dementia.

memory impairment that characterizes AD, the memory deficit in pure LBD usually appears later in the disease course [18]. This is consistent with the underlying neuropathology predominantly affecting frontal subcortical structures early on, and subsequent involvement of temporoparietal cortical structures as the disease progresses. However, there is variability in the literature with respect to memory performance, possibly because of the difficulty in isolating pure forms of LBD from LBD cases caused by concurrent AD pathology. LBD tends to co-occur with AD in 80% of cases, with only 20% having pure LBD. Patients with pure Lewy body pathology have better verbal memory skills than those with pure AD or mixed LBD/AD [19]. Patients with pure AD and mixed LBD/AD show equivalent degrees of impairment on verbal memory testing. By contrast, combined AD and Lewy body pathology appears to have an additive effect on visual memory skills [16].

Frontotemporal lobar degeneration is commonly the umbrella term used to describe three clinically, pathologically and genetically heterogeneous disorders with atrophy affecting the frontal and temporal lobes: behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia (PNFA) and semantic variant primary progressive aphasia (SV-PPA) [20]. BvFTD is generally characterized by a progressive deterioration of personality and social comportment, with relatively preserved episodic memory and no semantic memory impairment [21]. There is often marked variability in symptom profiles at initial presentation, which makes diagnosis of bvFTD a challenge. Revised diagnostic guidelines for bvFTD were recently published that accommodate the possible variations in symptom profile at initial presentation [22]. 'Severe amnesia' was previously an exclusion criteria for bvFTD; however, 10% of pathologically confirmed cases have reported memory symptoms at the time of the initial clinical evaluation [23], with some showing severe amnesia [24]. Current diagnostic criteria now cease to include severe amnesia as an exclusionary criterion, but rather include the overall neuropsychological profile in its entirety (i.e., executive function deficits with relative sparing of memory and visuospatial function) [23]. Generally speaking, mild difficulties across free recall measures can be noted but recognition memory is intact [25]. Unlike patients with AD, there is generally no rapid forgetting and the provision of cues can be helpful. The memory impairment of bvFTD is said to reflect diminished active strategies for learning and retrieval.

More recent studies have shown that prior inconsistent findings may be due to the inclusion of 'phenocopy' and not 'true' bvFTD patients, who are mainly indistinguishable from controls on neuropsychological testing. Phenocopy patients have behavioral symptoms consistent with true bvFTD patients, but they show relatively normal cognition, structural and functional imaging, and show little or no clinical change over many years [26]. The neural correlates of the memory impairment in true bvFTD and AD differs between the two patient groups. In the case of bvFTD, memory scores better correlate with frontal lobe atrophy rather than medial temporal lobe atrophy, as is seen in AD [27]. These findings suggest that contrary to prior thought, patients with bvFTD and those with AD may not be easily distinguished on the basis of their neuropsychological memory test scores.

Patients with SV-PPA differ from those with AD because they have relatively preserved episodic memory and autobiographical memory, with a rather selective loss of semantic memory [28,29]. PNFA produces a severe disruption of speech output (not typically seen in early AD), which is generally accompanied by mild episodic and semantic memory deficits [30].

Vascular dementia, considered to be one of the more common forms of dementia, is not ascribed to a single etiology as is the case with the typical AD dementia syndrome. Rather, it has different causes and clinical manifestations. A more homogeneous subtype of VaD identified in the literature is that of subcortical VaD. Subcortical VaD is a small vessel disease with dementia and constitutes approximately half of all VaD cases; this subtype is further classified into Binswanger's disease and multiple lacunar infarctions [31]. Some prefer the term vascular cognitive impairment as it is thought to reflect all possible effects of vascular disease or lesions on cognition, including those resulting from AD pathology with mixed cerebrovascular disease. In either case, VaD/vascular cognitive impairment can manifest with many clinical features, reflecting a variety of vascular mechanisms and changes in the brain, with different causes and different outcomes.

Generally speaking, VaD is a syndrome characterized by a relative abrupt onset (days to weeks), a stepwise deterioration (some recovery after worsening) and a fluctuating course (e.g., difference across days) of cognitive function temporally related to stroke(s). The cognitive symptoms may be mild and often include only mild, if any, episodic memory impairment, with some heteromodal cortical symptoms, such as aphasia, apraxia, agnosia and visuospatial difficulty. Some degree of executive dysfunction is also usually present, as well as focal neurological signs. The presentation of subcortical VaD tends to be more variable, with no consistent pattern of symptom onset or progression. Clinically, it is characterized by a subcortical cognitive syndrome, with primary deficits in executive functions and speed of information processing, and secondary deficits in episodic memory. Therefore, the memory impairment is less striking than in AD, characterized by impaired recall, relatively intact recognition, less severe forgetfulness and a greater benefit from cues [32–34].

It is well established that cognitive impairments are associated with depression in old age. Treating clinicians often question whether or not cognitive symptoms manifested by an older patient are symptomatic of a mood disorder that can be treated with antidepressants or indicative of the very early stages of an underlying neurodegenerative process, such as AD. Historically, the term dementia syndrome of depression or pseudodementia has been used to describe the reversible cognitive deficits experienced by some older patients suffering from late-life depression. Depression is a known risk factor for AD [35] and many patients with AD also develop depression at a relatively high rate [36]. The profile of scores on memory testing resembles that seen in subcortical VaD, with primary deficits in attention, executive functions, speed of information processing and secondary deficits in episodic memory. The memory impairment is milder than in AD and is characterized by impaired recall, relatively intact recognition, less severe forgetting

and greater benefit from cues. Moreover, AD patients tend to show greater false-positive errors during recognition memory testing, whereas depressed patients tend to use a more conservative approach, leading to more false-negative errors [37].

Language

Language impairment in the form of word-finding difficulties in spontaneous speech is well documented in AD. Such difficulties can be present at the time of initial evaluation. Individuals with AD are often impaired across measures of semantic memory, such as category fluency, word–picture naming and visual confrontation naming tasks [38–40]. They show a characteristic pattern of significantly worse performance on category fluency relative to letter fluency tasks, which is generally believed to arise from deterioration of the semantic memory system rather than from difficulties of access or retrieval from a relatively intact semantic store [41]. In more severe forms of AD, there is agrammatism, paraphasic errors, impoverished speech content and impaired comprehension. Prosody is affected in many patients, particularly in the more severe stages. In late stages, global aphasia or muteness is common. Those with PCA differ in that they show equivalently poor performance in category and letter fluency. Furthermore, those with PCA also show disproportionate difficulty on visual relative to verbal comprehension tasks, whereas those with typical AD show equivalent performance on the two tasks [41].

Patients with LBD show milder naming deficits than patients with AD on measures of confrontation naming, and there are group differences in this patient group from those with AD in terms of error profiles [42]. AD patients have been shown to make more semantic errors on an index of confrontation naming than patients with LBD [39]. By contrast, those with LBD make significantly more visuoperceptual errors on the Boston Naming Test than patients with AD [39]. The disproportionate visuospatial dysfunction described in LBD may contribute to a reduced ability to perceive objects accurately, leading to secondary errors in naming. Measures of generative fluency have also been proven to be useful in differentiating AD from LBD. LBD patients are equally impaired in category and letter fluency, whereas AD patients perform significantly better with letters than with categories [43,44].

By definition, SV-PPA affects knowledge about the meanings of words and objects. Brain imaging shows a characteristic pattern of atrophy involving the anterior portion of the temporal lobes that is almost always asymmetrical (left > right) [45], but inevitably becoming bilateral as the disease progresses. Patients with SV-PPA show greater semantic memory deficits than those with AD. They also have considerable comprehension deficits (seen in visual and verbal modalities) and like patients with AD, perform worse on category relative to letter fluency tasks. Patients with PNFA, on the other hand, show mild semantic memory impairment that contrasts with their severe disorder of speech production. The neural basis underlying this system is less well documented than that of SV-PPA, with studies showing involvement of the left inferior frontal lobe, particularly the anterior insula [46]. Unlike both SV-PPA and AD patient groups, those with PNFA and bvFTD do not show disproportionate deficits in category relative to phonemic fluency. Mutism occurs later in the disease course of SV-PPA and AD than in PNFA or bvFTD.

Logopenic progressive aphasia (LPA) is now recognized as an atypical focal language variant of AD. This disorder has been characterized as a primary phonological loop deficit leading to impaired memory, impaired sentence repetition and comprehension with slow spontaneous speech and long, frequent word-finding pauses [28]. From an anatomical perspective, brain atrophy accompanying LPA has a perisylvian distribution that overlaps with PNFA; however, studies have also emphasized a left temporo–parietal correlate in structural and metabolic neuroimaging studies [47].

Neuropsychological studies generally show a trend for patients with VaD to have lower output across measures of letter fluency than AD patients [48], possibly owing to increased problems with executive set maintenance. Semantic fluency is comparatively better preserved in VaD [49], as are receptive language skills involving comprehension of single words and picture meaning [37].

Performance on a range of tests, including those that assess word–picture naming, category fluency, picture naming and picture sorting has been reported as lower among older depressed patients compared with healthy volunteers [50]. However, unlike in AD, the anomia probably reflects problems with effortful retrieval [51], rather than a breakdown in semantic memory [52].

Visuospatial skills

Visual–spatial impairments are often among the first symptoms noted in AD and can be manifested by individuals getting lost in familiar environments, forgetting where they placed their personal items, or difficulty driving or parking a car. Neuropsychological evaluations using tests requiring angle discrimination, object/face/color recognition, contrast sensitivity, mental rotation, complex figure copy or clock drawing show marked visuospatial and visuoconstructional impairments in this group [53,54]. Difficulties in these processes are not surprising given the known pathological processes affecting critical visual processing areas in the parietal and temporal lobes. Visual acuity is relatively spared, except in patients with the visual variant of AD. Those with the PCA show striking problems with visual-based tasks that are secondary to their visual-processing disorder [54,55]. Additional features of PCA include visual agnosia and features of Balint's syndrome (simulatanagnosia and optic ataxia) and of Gerstmann's syndrome [55,56].

Pronounced visuospatial difficulties is also a consistent finding in LBD [19]. Patients with LBD consistently show greater difficulties on tests of visuospatial processing relative to AD patients. These differences tend to be present earlier on in the disease course and they are observed across measures of constructional praxis, visually mediated subtests of intelligence testing batteries and visuospatial tasks with or without motor or speeded components [47]. On complex figure copy tests, performance of patients with LBD is known to be affected, partially by disrupted visual spatial perception and partially because of reduced frontally mediated skills, such as organization, planning and working memory.

Unlike patients with AD and LBD, those with bvFTD tend to perform rather well on tests of visuospatial skills. In fact, similar to memory-related performance, intact visuoperceptual skills are a supporting diagnostic feature for FLD. One study showed that performance on measures of verbal fluency and constructional praxis reliably discriminated between AD and those with bvFTD [57], which probably reflects the differences in pathology between the two dementia syndromes. Unlike in AD, bvFTD tends to spare the occipitoparietal cortical regions. Praxis tests may be affected by amotivational performance and perseverative drawings in bvFTD [34]. Visuospatial tasks requiring executive function, such as trail-making, are impaired at an early stage, but block designs may be preserved. Overall scores on measures of visuospatial ability tend to be higher among patients with bvFTD than with AD [58]. Examining error scores has proven helpful to differentiate the two disorders; while patients with bvFTD make more executive-like errors, those with AD make more spatially mediated deficits. There does not appear to be any reliable differences across the group of frontotemporal lobar degenerations.

Subcortical VaD can also affect visuospatial functions. The changes are usually mild, but can be more pronounced relative to AD, depending on the measures used. In one review of 11 studies that included both patient groups, eight out of the 11 studies reported no differences between the VaD and AD groups across a range of visuoconstructional measures (e.g., block-design tests, clock-drawing test or copy of a complex figure) [34]. Three out of the 11 studies found that the AD patients were less impaired, although in each case, the praxic aspects of the test were eliminated. The early cognitive syndrome of cortical VaD can include compromised visuoconstructional skills. Indeed, clinical features of VaD are highly variable depending on the nature and location of pathology, which may or may not be controlled for in some studies.

Although not as severe as in AD, low scores across measures of visuospatial ability can also be seen among older nondemented depressed individuals [59]. In fact, depressed patients showing early decrements on tasks of memory, visuospatial skills and executive functions are at greater risk for developing AD than patients without decrements in these three domains [60].

Attention & executive functions

The degree to which executive functions are disrupted in most cases of AD remains somewhat equivocal. Some studies suggest that in the typical AD dementia syndrome, executive functions are relatively preserved during the early stages of the disease [61], whereas others suggest that this domain is impaired to the same extent or more than other cognitive domains [62,63]. Clearly, as the disease progresses, marked executive dysfunction becomes apparent, with changes in abstract reasoning, concentration, calculations and sustained visual attention being most common. In more severe cases, poor judgment and planning, difficulty completing a task and alterations in personality become especially pronounced.

There is an atypical frontal variant of AD that is now widely recognized, with a neuropathological correlate of greater numbers of neurofibrillary tangles within the frontal lobes than is seen in patients with the typical amnestic presentation [64]. Severity of executive dysfunction disturbance has been shown to be a strong predictor of AD progression [65]. Patients with this focal frontal AD variant are often difficult to distinguish clinically from those with bvFTD, which may reflect the underlying pathology. Indeed, between 7 and 32% of patients diagnosed clinically with bvFTD were also found to have AD pathology at autopsy [66]. Recent findings suggest that subjects with dementia who present with greater executive impairment, but without prominent behavioral symptoms, are likely to have AD rather than bvFTD, especially if they show significant functional decline [60]. Over time, those with bvFTD develop more marked executive dysfunction that resembles that seen in AD [60]. One possibility is that those with more marked executive dysfunction may reflect a more advanced disease process involving the frontal lobes. Biomarker data may facilitate the discrimination of patients with frontal variant AD from those with bvFTD.

Marked attentional and executive function disturbance is central to the clinical presentation of patients with LBD. Attentional disturbance may serve as the basis of fluctuating cognition that is characteristic of LBD. Neuropsychological studies have shown varying results between the test scores on measures of attention in AD and LBD. Few studies have shown group differences on digit span tasks [67,68]. More consistent group differences emerge on more complex attentional tasks, such as those requiring mental control, visual search and set shifting, and visual selective attention. On cancellation tasks, regardless of whether letters or shapes are used, LBD patients perform more poorly than AD patients. LBD patients are also more susceptible to distraction and have difficulty engaging in a task and shifting from one task to another. They tend to perform worse on Stroop, card sorting and phonemic verbal fluency tasks than comparably demented AD patients [69].

On a neuropsychological level, discriminating bvFTD from AD on the basis of executive test performance has yielded inconsistent results [70,71]. This is not entirely surprising given the widespread frontal atrophy and behavioral disinhibition that characterizes bvFTD that is probably difficult to capture. In fact, at the time of initial evaluation, bvFTD patients often perform in the normal range on traditional executive function tests measuring working memory, planning, mental flexibility, response inhibition and concept formation [72]. One meta-analysis reported that none of the measures of concept formation, problem solving or reasoning showed large group differences between AD and bvFTD [73]. Similar degrees of impairment between bvFTD and AD have also been noted using the Stroop and go/no-go tasks [74]. However, more recent findings show that a combination of orbitofrontal cortex atrophy and error scores on a measure of inhibitory control appears to be a powerful diagnostic tool in differentiating bvFTD from AD patients [75]. Self-monitoring is also another aspect of executive functioning that may be specifically disrupted in bvFTD but not in AD [76].

Typically, comparisons of patients with AD versus VaD on measures of simple attention (e.g., digit span) fail to reveal group differences [32,33,34]. However, with increased task complexity, and more

demands placed on sustained attention or mental set, vigilance and working memory, patients with VaD demonstrate greater deficits than AD patients [32,33,34]. Most studies of letter fluency show no difference or a slight superiority by patients with AD versus VaD [32].

Some of the well-replicated findings among older adults with depression are that of reduced processing speed, attention and concentration disturbance, and executive dysfunction. Many of these impairments remain present even after amelioration of depressive symptoms and may predict treatment response [77]. Executive failures in late-life depression are thought to be broadly related to cognitive slowing and frontostriatal abnormalities [78].

Lack of insight/unawareness/anosognosia

Lack of insight, unawareness or anosognosia are terms used to describe the impaired judgment of patients with dementia concerning their personal cognitive, mood and behavioral state. Estimates of the prevalence of anosognosia in AD are high, at approximately 80% [79]. Anosognosia occurs early in some AD patients, is variable for different domains, and has been shown to correlate with overall disease severity [80]. In line with this, patients with mild AD tend to be more anosognosic than those with MCI [81]. Loss of insight has been reported to be more impaired in BV-FTD than in patients with AD [82], and tends to be greater for personality and language changes [83]. Less is known about awareness of cognitive or behavioral deficits in patients with LBD. There is some evidence showing that patients with AD tend to show more anosognosic symptoms than those with LBD [84,85]. Patient complaint of deficit is often used clinically to distinguish VaD and depression from AD. That is, unlike in AD, there is relative preservation of insight in both VaD and depression [86]. In fact, the high prevalence rate of depression among VaD patients is thought to be the result of their preserved insight into their cognitive and noncognitive changes.

Behavior, mood, personality & psychiatric symptoms

Although cognitive deficits have traditionally been emphasized, a wide spectrum of neuropsychiatric symptoms occur throughout the course of AD; these symptoms represent a major source of disease morbidity. Neuropsychiatric disturbances have been associated with more rapid cognitive decline, increased caregiver burden [87], rises in patient care costs, greater medication use and adverse side effects, and wide-ranging institutional staffing needs given the higher numbers of earlier institutionalization of AD patients [88]. Overall prevalence rates of neuropsychiatric symptoms in AD range between 60 and 80%, and a lifetime risk of 90% or greater [89].

Common symptoms include mood disturbances, delusions, hallucinations, vegetative symptoms and aberrant motor disturbance. Delusions tend to be most common in the middle stage of the disease and center around themes of theft as a consequence of deficient memory. Visual hallucinations are a more common occurrence in PCA and they are usually well-formed, recurrent, spontaneous and nonfleeting [90], much like those in LBD. Patients with AD also develop depression at a relatively high rate, and it is typically marked by anhedonia and dysphoria [31]. Many of these symptoms are episodic, and in some cases, can precede the diagnosis of AD [91].

Lewy body dementia patients are more likely to show psychiatric symptoms and have more functional impairment than AD patients at the time of initial evaluation. In an analysis of autopsy-confirmed cases, hallucinations and delusions were more frequent with Lewy body pathology (75%) than AD (21%) at the time of the initial clinical evaluation [92]. This was also true for those cases with mixed LBD and AD (53%) pathology relative to AD alone. Delusions tend to be more common in LBD than in AD and they tend to be related to visual hallucinations and perceptual problems. By the end stages of both illnesses, there may be a comparable degree of psychotic symptoms in LBD and AD [93]. Depression is common in LBD and there is equivocal evidence as to whether base rates of depressed mood and major depression differ between LBD and AD [94,95].

Given that bvFTD is largely diagnosed by the presence of behavioral symptoms, it is somewhat circular to compare bvFTD with AD on defining features. Nevertheless, bvFTD is associated with higher levels of apathy, disinhibition, euphoria and aberrant motor behavior than AD [96]. BvFTD is also contrasted with AD by relatively greater emotional blunting and lack of empathy, poor personal hygiene, hyperorality and stereotyped behaviors [97,98]. Qualitatively, the depression in bvFTD differs from that in AD in that it is associated with more irritability and agitation. Results are mixed regarding the prevalence of aggressive behaviors. There are no differences in the prevalence of hallucinations or delusions between bvFTD and AD [97].

Affective features are very common in VaD. Depression, psychomotor retardation and abulia are believed to be more characteristic of patients with VaD than AD, even when matched for dementia severity [99]. The increase of affective disorders in VaD compared with AD is ascribed to the prominent involvement of frontostriatal circuits in VaD, central in the regulation of mood.

Personality

Changes in personality among AD patients have been well documented in the literature. Personality traits described for AD include neuroticism [100], decreased conscientiousness [101], increased rigidity and egocentricity [102] and coarsening of affect [103]. Personality traits may improve diagnostic accuracy in AD over and above that offered by cognitive test scores [104]. Furthermore, changes in personality may occur in the very earliest stages of AD, prior to the onset of any obvious cognitive decline [105].

Personality changes in LBD tend to occur with auditory and visual hallucinations, and include diminished emotional responsiveness, resignation of hobbies, increased apathy and purposeless hyperactivity [106]. Using principal components analysis, Galvin and his colleagues were able to identify three general personality traits in LBD [106]. The first were irritable traits and included increased rigidity, egocentricity, loss of concern, coarsening of affect and impaired emotional control; this accounted for almost 33% of the variance. The second were a passive group of traits and included diminished emotional responsiveness, relinquished hobbies, growing apathy and purposeless activity; this explained just over 12% of the variance. The third reflected disinhibition and included inappropriate hilarity and sexual misdemeanor; this explained an additional 10.4% of the variance. Using this

three-factor structure, patients with LBD were more likely to manifest personality traits associated with passive personality traits than patients with AD. Using receiver operating characteristic curves, these authors also showed that the passive personality traits discriminated between AD and LBD, whereas both the irritable set of traits and those reflecting disinhibition were uncommon in both groups.

Personality changes appear to be more common in bvFTD than in AD and may assist with the differential diagnosis of AD from bvFTD. BvFTD patients often show more antisocial and apathetic behavior than AD patients and show a greater loss in their sense of self [107]. In a recent meta-analysis, strong group differences emerged on an Empathy Index, with the bvFTD group displaying less empathy than the AD group [96].

Extrapyramidal symptoms

Extrapyramidal symptoms (EPSs) are a common feature of AD. These symptoms appear to increase over time with disease severity [108] and are the strongest independent predictor of severity of depression [109]. EPSs are more common in LBD than in AD [92]. AD patients also have a lower risk of developing EPSs with the use of typical neuroleptics relative to those with LBD [110]. Several studies suggest that LBD and AD cannot be reliably distinguished solely on the basis of spontaneous EPSs. EPSs in bvFTD are associated with a specific endophenotype (suggesting mutations in the tau gene located on chromosome 17), characterized by higher incidence of psychotic symptoms, memory deficits and psychomotor speed abnormalities [111]. Recent research indicates that EPSs are also commonly found in patients with PPA and LPA and rare in SV-PPA. Early phases of subcortical VaD can also include EPSs such as hypokinesia and rigidity. While most aspects of EPSs are not found in depression, psychomotor slowing in more severe cases of depression can be mistaken for bradykinesia.

Expert commentary & five-year view

A total of 100 years has passed since the appearance of the first article on AD by Alois Alzheimer. AD is the most common form of dementia, accounting for 50–75% of all dementia and affecting more than 26 million people worldwide. Over the past three decades, we have witnessed an explosion of research

Table 2. Cognitive profiles of common causes of dementia.

Cognitive domain	AD	Lewy body dementia	Behavioral variant frontotemporal dementia	Vascular dementia	Depression
Episodic memory					
Free recall	+++	++	+/-	+	+
Recognition	+++	-	-	-	-
Prompting	x	✓	✓	✓	✓
Intrusions	+++	+++	+++	+	+
Semantic memory (naming)	++	+	+	+	+/-
Procedural memory	-	+	-	+	+
Working memory	++	+++	+++	++	+/-
Insight	+++	+	+++	-	-
Attention	++	+++	++	++	+++
Executive functions	++ typical AD +++ frontal variant	+++	+++	+++	++
Visuospatial skills	++ typical AD +++ PCA	+++	-	+	+

+++ Early and severe impairment.
++ Moderate impairment.
+ Mild impairment.
+/- Impairment in some studies but not others.
- No significant impairment.
x Not helpful.
✓ Helpful.
Note: +++ Behavioral variant frontotemporal dementia patients often perform in the normal range on traditional executive functions tests measuring working memory, planning, mental flexibility, response inhibition and concept formation, although this may reflect the difficulty in capturing specific 'frontal lobe' functions on standard executive function measures.
AD: Alzheimer's disease; PCA: Posterior cortical atrophy.

effort dedicated to the study of AD, with some speculation that disease-modifying therapies are on the horizon. Biomarkers play an increasingly important role in AD drug development and will continue to be refined moving forward. AD together with the other major neurodegenerative syndromes remain a major public health problem. The early detection, prediction and dissociation of dementia syndromes is, therefore, of paramount interest, especially for treatment purposes.

The typical AD syndrome can be characterized by prominent episodic memory impairment, with secondary deficits in word-finding skills, spatial cognition and executive functions. While hippocampal dysfunction is presumed to underlie memory impairment in AD, memory impairment can also manifest because of frontal lobe atrophy affecting active search and retrieval skills, as is the case in true bvFTD. Relatively less is known about the clinical presentations and natural progression of the atypical variants of AD. PCA can resemble LBD. LPA and PFNA share common features, as does the frontal variant AD and bvFTD. Co-occurrence of cerebrovascular disease and Lewy body pathology is not uncommon in the brains of people with AD, which inevitably complicates clinical diagnosis. Depending on the areas and extent of pathology, patients with VaD can show diverse clinical signs and symptoms. What is currently lacking is a single behavioral marker that can reliably discriminate AD from other dementia syndromes. Neuropsychological testing has been proven to be useful in the differential diagnosis of dementia (see Table 2 for a summary of the neuropsychological deficits across the dementias). However, the large overlap in the test performance of individuals diagnosed with AD and the other dementia syndromes suggests that neuropsychological measures should be used cautiously and in conjunction with other features, such as medical history, behavioral observations, biomarker data and information from collateral sources, when making differential diagnoses. Future studies should focus on identifying new approaches that can easily be used in clinical and/or research situations and at a low cost to assess cognitive and neuropsychiatric symptoms among older patients in the early stages of dementia.

Key issues

- Alzheimer's disease (AD) is the most common form of dementia. There are 35 million individuals worldwide currently affected by the disease; and AD is projected to affect 115 million by 2050. Generally speaking, AD neuropathology initially involves medial temporal lobe structures (e.g., hippocampus and entorhinal cortex) and subsequently extends to temporal, parietal and frontal lobe association areas as the disease progresses. Neuropsychiatric symptoms are present throughout the course of AD.
- New diagnostic criteria for AD emphasize the importance of biomarker data in the definition of prodromal AD. The typical dementia syndrome continues to be described by prominent episodic memory impairment linked to early changes in the hippocampus and entorhinal cortex, with secondary deficits in word-finding skills, spatial cognition and executive functions.
- Atypical presentations of AD include posterior cortical atrophy, logopenic progressive aphasia and focal frontal variant AD. In posterior cortical atrophy, the onset is characterized by early, higher-order visual deficits and a higher density of neurofibrillary tangles in the occipital regions than in typical AD. Logopenic progressive aphasia is an atypical language variant defined as a primary phonological loop deficit leading to impaired memory, sentence repetition and comprehension, with sparse spontaneous speech and frequent prolonged word-finding pauses. Greater numbers of neurofibrillary tangles within the frontal lobes are seen in frontal variant AD, resulting in a more severe disease course.
- Episodic memory scores do not differ between behavioral variant frontotemporal dementia patients and AD patients, although the neural correlates of the memory impairment differs between the two patient groups.
- Lewy body dementia (LBD) tends to co-occur with AD in 80% of cases, with only 20% having pure LBD. Patients with pure Lewy body pathology have better verbal memory skills than those with pure AD or mixed LBD/AD.
- A fluctuating or step-wise course and history of strokes may help clinicians differentiate AD from mixed AD with cerebrovascular disease when their clinical profiles are otherwise indistinguishable. Subcortical vascular dementia is associated with primary deficits in information processing speed and executive functions, and secondary milder effects on memory.
- Personality changes are common among the dementias. They can occur in the very earliest stages of AD, prior to the onset of any obvious cognitive decline and can discriminate between AD and LBD (more passive traits in the LBD group). Personality changes appear to be more common in behavioral variant frontotemporal dementia than in AD.
- Current treatments for AD provide symptomatic relief either by improving symptoms or by delaying decline. Improving our understanding of the molecular mechanisms of AD has led to the identification of multiple potential targets for disease-modifying agents.

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Medscape EDUCATION

Distinguishing Alzheimer's disease from other major forms of dementia

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. Your patient is a 73-year-old white woman with a recent history of forgetfulness. Based on the review by Drs. Karantzoulis and Galvin, which of the following features would be **most likely** characteristic of classical Alzheimer disease (AD)?

- ☐ **A** Sudden onset of forgetfulness
- ☐ **B** Rapid progression of forgetfulness over 2 weeks
- ☐ **C** Prominent episodic memory impairment with secondary deficits in word-finding skills, spatial cognition, and executive functions
- ☐ **D** Neuropathology predominantly involving the occipital cortex

2. Based on the review by Drs. Karantzoulis and Galvin, which of the following statements about atypical presentations of AD and non-AD dementias is **most likely** correct?

- ☐ **A** AD almost never co-occurs with other dementia pathologies
- ☐ **B** Posterior cortical atrophy is pathologically distinct from AD
- ☐ **C** Episodic memory scores differ dramatically between patients with frontotemporal dementia and those with AD
- ☐ **D** In logopenic progressive aphasia, a primary phonologic loop deficit leads to impaired memory, sentence repetition, sparse spontaneous speech, and prolonged word-finding pauses

3. The patient described in question 1 undergoes diagnostic evaluation to determine the cause of dementia. Based on the review by Drs. Karantzoulis and Galvin, which of the following statements about the significance of various diagnostic findings is **most likely** correct?

- ☐ **A** Primary deficits in information processing speed and executive functions and secondary milder memory effects suggest subcortical vascular dementia
- ☐ **B** More passive personality traits suggest AD rather than Lewy body dementia (LBD)
- ☐ **C** Autosomal dominant genetic mutations of PSEN1 or PSEN2 support the diagnosis of LBD
- ☐ **D** AD biomarkers are not required for diagnosis because the behavioral profile of AD is distinctive