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ABSTRACT

The neurocognitive and behavioral profiles of vascular dementia and vascular cognitive impairment, dementia with Lewy bodies and Parkinson's disease with dementia, and dementia syndromes associated with frontotemporal lobar degenerations are compared and contrasted with Alzheimer's dementia (AD). Vascular dementia/vascular cognitive impairment is characterized by better verbal memory performance, worse quantitative executive functioning, and prominent depressed mood. Dementia with Lewy bodies and Parkinson's disease with dementia are equally contrasted with AD by defective processing of visual information, better performance on executively supported verbal learning tasks, greater attentional variability, poorer qualitative executive functioning, and the presence of mood-congruent visual hallucinations. The frontal variant of frontotemporal lobar degeneration (frontotemporal dementia) differs from AD by better multimodal retention on learning tasks, different patterns of generative word fluency, defective qualitative executive functioning, and by markedly impairment of comportment. For temporal variants of frontotemporal lobar degenerations, progressive aphasia and semantic dementia, worse language performance relative to AD is typically characteristic. (*J Geriatr Psychiatry Neurol* 2007;20:227-238)

Keywords: dementia; neurodegenerative; cognitive impairment; vascular; Lewy body; frontotemporal; Alzheimer; Parkinson's disease with dementia

A major public health issue facing the "baby boom" generation of the 21st century will be the economic consequences of rapidly increasing dementia incidence and prevalence.[1] Although Alzheimer's dementia (AD) is the most common type of dementia, accounting for between 50% to 75% of all late-life dementias,[2] there will be significant increases in other forms of dementia, namely vascular dementia (VaD) as well as vascular cognitive impairment (VCI), dementia with Lewy bodies (DLB) and associated Parkinson's disease with dementia (PDD), and frontotemporal lobar degenerations (FTLDs). Key advances have been made in understanding the genetics, pathophysiology, and biological indicators of Alzheimer's disease. As a result, multiple agents currently are either in development, or clinical trials that target the beta-amyloid pathway related to Alzheimer's disease currently are either in active clinical trial or development.[3] Similar scientific advances are being made in understanding the causes of the other neurodegenerative dementias, which hopefully will result in disease-specific medications for these disorders. Our understanding of the cognitive and behavioral profiles of these neurodegenerative disorders, however, lags behind that of Alzheimer's disease. This review is designed to help fill this knowledge gap.

Alzheimer's disease has become the gold standard against which other dementing illnesses are compared. The cognitive-behavioral profile of AD is well characterized and reviewed briefly here to frame the benchmark standard. The calling card for AD is memory loss featuring profound anterograde amnesia. New information is rapidly forgotten as a result of bilateral medial temporal lobe damage that severely reduces the ability to encode

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and consolidate new information.[4] Heteromodal cortical association cortex is progressively involved with an affinity for posterior parietal and temporal regions, although dorsolateral prefrontal cortex is often involved as well.[5] As a result, problems with spatial processing, executive dysfunction, and faulty semantic knowledge are increasingly manifest as the disease progresses. Language and speech become anomic and void of meaning with preserved fluency, articulation, and grammar. Topographical disorientation is a frequent functional correlate of diminished spatial capacity. Behaviorally, social graces and conduct are well preserved into the middle stages of AD. As AD progresses in severity, up to a third of patients suffer from paranoid delusions that often center on themes of theft as a consequence of defective memory.[6] Up to a third of AD patients also suffer from mood disturbance. When present, depression in AD is typically associated with dysphoria and anhedonia. Increased anxiety often involves separation issues and fears of abandonment regarding the primary provider of informal care.

VCI/VaD

The distinction between the neuropathology associated respectively with VaD and the plaques and tangles that came to be known as Alzheimer's disease was first noted by Kraepelin in 1896.[7] Although VaD resulting from atherosclerosis was initially thought to be the leading cause of dementia in late life, the work of Tomlinson et al in 1970[8] began to shift the focus to Alzheimer's disease as the most frequent cause of dementia, and VaD was largely restricted to instances of what Hachinski et al[9] described as multi-infarct dementia. Today, there is a resurgence of interest in vascular causes of cognitive impairment,[10,11] and VaD is generally recognized as a common form of dementia in older persons,[10] with conservative estimates of 1% to 4% of individuals aged 65 suffering from VaD and the prevalence doubling every 5 to 10 years[12]; however, these figures may underestimate the contribution of vascular factors to the emergence of dementia for a number of reasons, not the least of which are: (1) definitions of VaD are modeled after the neurocognitive features of AD, which emphasize deficits of new learning and memory rather than the psychomotor slowing and deficits of executive function that are common in vascular syndromes,[13] and; (2) cerebrovascular disease often overlaps with other pathologies (especially Alzheimer's disease), resulting in mixed dementias and thereby causing or contributing to up to 80% of dementias in old age.[14]

Although VaD conceptually can be defined as any dementia resulting from vascular disease, it is the endpoint of a much more complex and varied process.[15] Recently, the term VCI has been proposed to describe the broad spectrum of cognitive and behavioral changes, including VaD, associated with vascular pathology that are of sufficient severity to meet criteria for a diagnosable disorder.[16] Libon et al[17] have proposed that variations in VCI can be characterized on the basis of whether vascular disease is extracranial or intracranial. Extracranial vascular disease involves thrombi, emboli, or atherosclerosis that block 1 or more of the 3 major cerebral arteries, resulting in abrupt changes in cortical functions and stepwise progression characteristic of poststroke dementia and multi-infarct dementia. Changes associated with intracranial vascular disease progress in a more insidious manner and involve either the long penetrating arteries from the surface of the brain, affecting the cortical white matter, or the subcortical ventriculofugal vessels that support the basal ganglia, thalamus, and internal capsule, affecting the subcortical and periventricular white matter characteristic of Binswanger's disease (ie, leukoariosis) and lacunar states. In addition, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and cerebral amyloid angiopathy also contribute to structural alterations of the arterioles supplying the subcortical white matter.

VCI/VaD VERSUS AD

Because definitions of VaD have been modeled after AD, there is still an emphasis on impairments of memory and other cortical functions (eg, language, praxis, gnosis, and movement), rather than on the psychomotor slowing and executive deficits typically associated with disruptions of the subcortical-frontal circuits that are frequently seen in VCI and VaD.[13] Certainly, extracranial vascular disease involving the major cerebral vessels can result in cortical deficits depending on the location of the stroke, and strategically located single or multiple infarcts involving the territories of posterior and anterior cerebral arteries, basal ganglia, and especially the thalamus disrupt memory and double the risk of dementia[18]; however, when "cortical" deficits occur in the context of intracranial small vessel ischemic disease, some authors suggest that concomitant Alzheimer's disease should be considered.[19] Examination of the literature concerning VCI, especially as it relates to small vessel ischemic changes, does reveal some phenotypic patterns.[10,17,20]

Attention and Executive Functioning

Typically, comparisons of patients with AD versus VCI or VaD on measures of working memory requiring simple attention and tracking fail to reveal group differences[21-24]; however, as tasks become more complex and require sustained attention or mental set, vigilance, and cognitive flexibility, patients with VCI demonstrate greater

deficits than AD patients.[17,22,25,26] Although these findings suggest that AD and VCI patients have comparable levels of arousal and response orientation, VCI results in greater executive deficits caused by disruption of the frontal-subcortical circuits.

Studies that have explicitly examined executive functions typically find patients with AD superior to individuals with VCI and VaD on general measures of new concept formation,[27,28] initiation and freedom from perseveration,[26,28-31] and planning and self-regulation.[24] Libon et al[17,25,32,33] argue that these abilities require one to understand and appreciate task demands and respond to the demands until the task is completed and then to shift set when the task demands change. Although most studies of behavioral fluency show no difference or a slight superiority by patients with AD versus VCI,[22,23,26,30] patients with VCI show greater within-trial decrements in performance over time,[32,33] suggesting problems with set maintenance. They also manifest greater difficulties shifting between sets on paradigms of graphical sequencing and complex card sorting.[25,28,31]

Episodic Memory

Patients with VCI and VaD typically demonstrate more intact immediate and delayed memory functions than those with AD, especially on verbal memory tests of story recall[23,24] and various forms of list learning.[23,34,35] Even when patients with VCI have difficulty with recall, they demonstrate superior recognition and cued recall compared with AD[25,26]; however, although VCI patients are superior to individuals with AD on declarative verbal memory tests, they perform more poorly than AD patients on procedural memory paradigms such as pursuit motor learning where they show less time on target and have difficulty carrying learning forward on subsequent trials, possibly because of disruption of thalamic-neostriatal-frontal lobe circuits.[36] Few differences between VCI/VaD and AD have been noted on nonverbal measures of visuospatial memory,[37] figural memory,[23,24] or facial recognition memory.[38] The discrepancy between verbal and nonverbal memory functions is most likely caused by a more general breakdown in lexical and semantic networks in AD.[39] Overall, it would appear that AD results in greater difficulties in verbal learning, rapid forgetting, and little benefit from cued recall and recognition compared with VCI; however, although Kramer et al[30] found more rapid forgetting in AD, there was considerable variability among VCI patients, with some showing good retention but poor executive functions and others who had poor retention but better executive skills. They found that good retention was correlated with greater lacunar involvement on MRI and suggested that patients with vascular disease and rapid rates of forgetting may have concomitant AD. Reed's research group also raises similar concerns.[40]

Language-Related Processing

Looi and Sachdev[20] found few differences in general intelligence in their review of patients with VaD and AD, although some investigators have reported superior verbal intelligence in VaD.[21,41] Looi and Sachdev[20] also found no differences between VaD and AD in early studies of confrontation naming, letter fluency, or auditory comprehension; however, more recent studies of phonemic fluency that incorporated newer imaging techniques have shown a trend for VCI patients to have lower output than AD,[22,39] possibly because of increased problems with executive set maintenance.[17] Nevertheless, because semantic networks mediated by the mesial temporal regions are particularly affected in AD, semantic fluency is comparatively better preserved in VCI.[25,39] Receptive language skills involving comprehension of single words and picture meaning have been reported to be better preserved in VaD,[42] whereas individuals with AD are superior on simple measures of reading and writing.[29,43]

Visual Information Processing

Generally, AD and VaD patients do not differ significantly on most measures of constructional praxis and visuomotor problem solving.[21,23,24] Impaired performance on clock drawing tasks has been equivocal, with no differences being reported in some studies[25,26] and AD superiority in others.[26,32] Royall et al[44] suggest that clock drawing errors reflect not only problems with constructional praxis, but also deficits related to executive control functions mediated by the frontal cortex and its basal ganglia-thalamic connections, regions often affected by subcortical vascular disease. No differences between AD and VaD patients have been reported for nonmotor tasks of visual discrimination and spatial orientation,[30,38] figure ground discrimination,[41] or visual organization.[24]

Behavioral/Psychiatric Symptoms

Depression commonly occurs within the first year post-stroke in about 33% of patients,[45] and depression, psychomotor retardation, and abulia are believed to be characteristic of patients with subcortical VCI.[46] A comparison of patients with AD and VaD, matched for dementia severity, demonstrated greater behavioral retardation, anxiety/depression, and reduced verbal output in the VaD subjects, with a third showing signs of blunted affect, depressed mood, emotional withdrawal, motor retardation, low motivation, somatic concerns, and anxiety.[47] Schneiber[48] suggested that late-onset depression may foreshadow the development of dementia and may be related to small vessel ischemic changes in the

subcortical and periventricular white matter, especially in the left frontal regions. Indeed, recent research[49] suggests a bidirectional relationship between depression and vascular disease, with depression in patients younger than 65 having a 4.2 increased risk of stroke.

DLB

Over the course of the last decade, DLB has emerged as a clinical diagnosis with a neurocognitive and behavioral profile that is distinct from that of Alzheimer's disease. Lewy bodies (LBs) are α-synuclein neuronal inclusion bodies that can be found in multiple neocortical, limbic, and brainstem areas.[50-52] Although they were first described nearly a century ago by Friedrich Lewy in the brainstem of patients with Parkinson's disease (PD),[53] case reports of cortical LBs associated with dementia did not appear until nearly 50 years later.[54] DLB is characterized by prominent deficits in visuospatial ability, attention, and executive functioning, as well as the possible absence of marked early course memory changes.[55] Core DLB diagnostic features are fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations that are typically well formed and detailed, and spontaneous motor features of Parkinsonism.

LBs are associated with up to 25% of autopsies in older adults with dementia, second only to Alzheimer pathology among neurodegenerative disorders.[52] Nevertheless, the boundaries between DLB and both AD and PDD remain unresolved. The pathologic presence of pure DLB is relatively rare because there is a pronounced co-occurrence of LBs and Alzheimer's pathology.[56] At the same time, however, the appearance of DLB core features is significantly reduced when LBS and Alzheimer's pathology co-occur.[57] Moreover, the evolving pathology-based definition of Alzheimer's disease[58,59] has blurred direct comparison between DLB and AD on several autopsy series. Although DLB and PDD are associated with different initial symptom presentations, both behavioral and biological similarities outweigh differences between these disorders.[51,55]

DLB VERSUS AD

Visual Information Processing

DLB is associated with profound impairment in both the spatial and perceptual networks of visual information processing.[60] DLB patients consistently perform worse than AD patients on tasks of perceptual processing, such as abstract form discrimination.[61-66] In addition, an association between perceptual impairment and visual hallucinations in DLB may imply directionality between the nature of perceptual disturbance and hallucinatory content.[64,65,67] DLB-related deficits are commonly found on traditional measures of visuospatial processing, including on measures of constructional praxis,[66,68-76] visually oriented subtests of intelligence testing batteries,[74,77-80] and visuospatial tasks without motor or speeded response demands.[61,64,66,73,77,81] Of note, results showing overall equivalent visuospatial performance between groups have indicated greater DLB-associated executive errors (eg, planning/organization) on qualitative analysis.[67,71] Such findings are consistent with the relative paucity of LBs in parietal and especially occipital cortex, but a catastrophic loss of cholinergic and dopaminergic pathways to these regions because of a massive preponderance of LB pathology in downstream brainstem regions.[50]

Attention and Executive Functioning

Although impaired attention is a cardinal sign of DLB, the measurement of attention poses a challenge. Verbal attention span has been widely used; however, although some studies show a significant DLB effect on digit span relative to AD on some studies,[61,73,76,82,83] a span effect has proven elusive in other studies.[68,70,83] Standardized neuropsychologic measures of attention that combine the components of selection, vigilance, and executive control of attention have more consistently resulted in DLB-specific attention impairment.[61,62,73,81] Perhaps the most promising line of research is with computerized batteries of attention, where patients with DLB have shown greater response variability on all attentional components and a greater decrement on the executive control of attention.[84-87] Of great interest, attention-based reaction time variability is significantly correlated with questionnaires of fluctuating cognition and electroencephalogram-measured fluctuations,[87] suggesting that attentional variability may be a useful measure of fluctuating cognition in DLB. Moreover, these computer-based paradigms of attention are easily administered, such as choice reaction time (stimulus selection: absence vs presence) and digit vigilance (single stimulus-sustained attention).[85,87]

Empirical data on executive dysfunction in DLB are difficult to obtain on standardized neuropsychologic measures heavily dependent on intact graphomotor and visual processing ability. For example, DLB patients perform worse than their AD counterparts on both parts of the Trailmaking tests that hold motor-based response demands equal between parts,[73,78,88] although Trails B (requiring simultaneous graphomotor number and letter sequencing) was selectively impaired in a recent large-scale autopsy series for LB presence without concomitant Alzheimer's pathology.[82] DLB patients, however, have considerable difficulty on tasks of phonemic fluency (as detailed later here) and performing dual

tasks (digit span and symbol cancellation).[61] Doubleday et al[89] used an innovative behavioral rating system on which DLB patients showed significantly more qualitative executive impairment as compared with AD patients independent of the target domain being tested, including greater distractibility, poor mental set establishment and shifting, circumstantial thought, total extratest intrusions, and perseverative responses. The executive/attentional vulnerability of DLB likely is a direct result of prominent LBs widely distributed in frontal networks, including the frontal lobes, cingulate cortex, and dopaminergic subcortical nuclei.

Episodic Memory

DLB patients show a pattern of poor initial acquisition of new material but relatively better delayed recall or retention/savings at delay as well as improved recognition scores. DLB patients have outperformed AD on verbal measures of word-list learning,[62,73,78,90-93] but not all studies employing word-list learning or word-recognition paradigms result in a DLB advantage.[61,69,81] In contrast, DLB patients consistently demonstrate an advantage over AD patients on delayed-recall and retention measures of logically constructed story passages.[61,74,77,78,81,82,90] The discrepancy between word-list and story learning may best be understood by the contextual benefit conferred by story-related information, whereby context-bound information likely helps compensate for the executive deficit in DLB. Nevertheless, on visual learning measures, there is either an advantage for AD[62,74] or no difference between the patient groups.[61,65] When a DLB-related relative disadvantage does emerge on visual learning measures, the deficit most likely reflects spatial and perceptual problems that selectively interfere with encoding.[60,83] There is a differential distribution of pathology in the hippocampus between the 2 disease processes that might support these differences. Whereas Alzheimer's pathology tends to accumulate primarily in the CA1 region of the hippocampus, LBs aggregate in CA2/3 hippocampal areas.[90]

Language-Related Processing

Roughly equal numbers of studies show either equivalence between DLB and AD on confrontation naming[61-63,73] or a DLB advantage.[65,78,82] On measures of generative verbal fluency, semantic production is equally impaired between the groups, whereas phonemic fluency tends to be significantly deficient in DLB relative to AD.[61-63,73,74,77,78,83] This difference likely reflects the greater executive load of phonemic versus semantic/categorical word generation, and although DLB is associated with equal within-group impairment between semantic and phonemic fluency, Alzheimer patients demonstrate a semantic disadvantage on generative word fluency. When present, language-related deficits in DLB likely are secondary to the amount of perceptual/spatial and executive demands of the task, either singly or in combination.[63]

Behavioral/Psychiatric Symptoms

Psychotic symptoms of any type are more common in DLB than AD. The 4 most frequent psychotic symptoms in DLB are as follows: visual hallucinations (54%), delusions (49%), auditory hallucinations (25%), and olfactory hallucinations (7%).[83] In contrast, delusions were the most common psychotic symptom in Alzheimer's disease (31%), with much lower rates of all types of hallucinations: visual (23%), auditory (6%), and olfactory (3%). Whereas AD-associated delusions tend to be secondary to the amnesia (eg, paranoia around theft and misidentification), delusions in DLB are more related to visual hallucinations and perceptual problems, such as phantom boarder and Capgras syndromes; however, the overall rate of psychotic symptoms in AD catches up with DLB as a function of greater dementia severity.[67] Although depression is common especially early in the course of DLB, there is equivocal evidence as to whether base rates of depressed mood and major depression differ between AD and DLB.[73,78,83,90,92,94]

DLB VERSUS PDD

There is considerable cognitive and behavioral overlap between PDD and DLB. PDD and DLB patients perform similarly on measures of attention and executive functioning,[62,85,92] perceptual and spatial ability,[62,66,72] learning and memory,[62,65] and rates of depression.[68,85] There is 1 report of significantly more psychotic features in DLB than PDD,[95] but this finding needs to be replicated. In fact, the term Lewy body dementias (LBDs) recently has been coined to capture the preponderance of similarities between DLB and PDD.[51] At the same time, however, the retention of the terms DLB and PDD has been recommended to classify separate clinical entities for the following reasons: (1) at least 1 year of motor symptoms without significant cognitive deficits (PD) best characterizes PDD; (2) the LBD pattern of cognitive deficits either in advance or presenting concomitantly with motor symptoms is a distinct phenomenology from either PD or PDD; and (3) even when present, visual hallucinations in PDD tend to be less frequent than in LBD.

FRONTOTEMPORAL LOBAR DEGENERATION

Although dementias associated with FTLD are associated with distinct patterns of topographic neurodegeneration and histopathology as compared with Alzheimer's

disease, their cognitive and behavioral profiles are somewhat surprisingly difficult to disentangle. Nevertheless, with the use of appropriate testing instruments, distinct patterns emerge when the varieties of FTLD are studied separately from each other and in contrast to AD. Current clinical diagnostic criteria[96,97] recognize 3 forms of FTLD, each associated with different areas of primary neurodegeneration[98]: (1) frontotemporal dementia (FTD), characterized by a marked disturbance in personality and social conduct and associated with bilateral or unilateral (right more than left) frontal lobe damage (with an emphasis on ventromedial damage); (2) progressive aphasia (PA), a disorder of expressive language that ultimately results in nonfluent speech production that is related to left-sided damage along the perisylvian cortex; and (3) semantic dementia (SD), which involves loss of semantic meaning evidenced by multimodal problems with naming and comprehension with an association to bilateral or unilateral (left more than right) anterior temporal damage (lateral and inferior). Although the FTLDs are associated with heterogeneous histopathology,[96] a major division is whether neurons stain positive (including the presence of Pick body inclusions) or negative (including Ubiquitin-positive inclusions and an absence of inclusion bodies) for the protein Tau.[99] Recent familial cohort studies have identified proximal but dissociable gene mutations on chromosome 17q21 that code for the Tau and Progranulin proteins (the latter of which also is associated with the protein Ubiquitin)[100-102]; to date, however, there is inconclusive evidence whether either of these genes is uniquely related to the clinical syndromes of FTD, PA, or SD.[103-105] The prevalence of the FTLDs ranges between 10% to 20% among the neurodegenerative dementias.[106]

FTLD VERSUS AS

Language-Related Processing

Qualitatively, language and speech patterns are among the most differentiable features between FTD, PA, and SD, but can be confused with a relatively rare presentation of language-predominant AD.[107-109] Although PA patients may have relatively preserved fluency early on,[109] the ultimate presentation is that of markedly reduced fluency progressing to mutism, reduced syntactical comprehension, phonologic errors, poor articulation, and agrammatism, which may closely correspond to a classic Broca's aphasia presentation.[107,108,110,111] FTD patients may share similar speech and language features as compared with PA,[42,107,112] yet reduced verbal output related to an overall pattern of poor initiation is the prominent language disturbance. Speech is fluent in SD, also known as fluent PA. In addition, SD is associated with comparatively preserved syntactical comprehension but with profound anomia and multimodal loss of semantic/conceptual comprehension.[98,107,110,111,113-119] In contrast, language deficits in AD are best described as fluent and anomic with a gradual loss of comprehension (for syntax and semantics), which at first is similar to a transcortical sensory aphasia but with increasing dementia severity comes to resemble a Wernicke's aphasia.[2,107] Mutism in both AD and SD appear comparatively later in the disease course than in either PA or FTD. Another type of primary PA has been described, namely logopenic PA (LPA).[112] LPA features impaired repetition as well as decreased overall fluency and rate of speech with preservation of articulation and phonology. Of considerable interest, LPA is associated with a posterior pattern of left-sided parietotemporal atrophy and a distribution of the apolipoprotein E ε4 allele that is very similar to that of AD,[108] suggesting that LPA may be tantamount to language-predominant AD.

Quantitatively across the published literature, the varieties of FTLD-related dementias and AD have proven difficult to distinguish because of studies conducted before the appearance of clinical criteria to separate the subtypes of the FTLDs, underpowered designs, and inconsistent use of sensitive tests. Although patients with unspecified FTLDs or FTD (FTLDs/FTD) do not differ from AD patients on global measures of comprehension,[120-122] comprehension failures appear to be more because of poorly understood syntax and executive influences (eg, concrete thinking) in the FTLDs and a combination of semantic, memory load, and praxis factors in AD.[42,121] Although both AD and FTLD patients show reduced comprehension and naming of verbs relative to nouns, early evidence pointed toward a greater action versus object discrepancy in the FTLDs[123,124]; however, this difference disappeared between a group of pure FTD (ie, without inclusion of PA or SD) and AD patients.[125] Nevertheless, among the FTLDs, poor action comprehension/naming is differentially associated with executive dysfunction in FTD, poor processing of syntax in PA, and defective understanding of semantics in SD.[126] In contrast, there is no evidence that performance on measures of object confrontation naming differentiates AD from either unspecified FTLD or FTD (ie, via autopsy confirmation).[42,111,113,116-122,127-131] Nevertheless, both PA and SD patients perform worse on object naming measures as compared with either AD or FTD.[98,110,111,113,115,118,119,131] Of possible note, Tau-negative FTLD is associated with significantly lower confrontation object naming as compared with Tau-positive FTLD.[99]

Generative verbal fluency may be of particular help in differential diagnosis because of the specific semantic processing demands of category fluency as compared with general executive demands inherent in both category and letter fluency.[132] As expected based on their cardinal language-related features, SD and PA groups

generally perform worse on category and letter generation tasks as compared with AD and FTD,[98,111,113-115,119] although there is some evidence that those with PA and SD demonstrate equally impaired generative word fluency regardless of word type.[111] Although categorical word generation is uniquely impaired compared with phonemic production in AD, the overall pattern is that category fluency is equally impaired between AD and FTLDs/FTD[42,98,111,114,115,117,119,127,133-135] with few exceptions.[117,130] On the surface, it appears that approximately equal numbers of studies have reported relatively lower phonemic fluency in FTLDs/FTD[114,117,122,124,128-130,136,137] or no difference between AD and FTLDs/FTD[98,111,115,118,119,121,133-135]; however, there are multiple methodologic concerns with these fluency studies, including small sample sizes, the use of clinical criteria that do not separate the FTLDs, and assaying fluency with only 1 exemplar class (which may not be a sufficiently sensitive behavioral measure[132]). The only 2 autopsy-confirmed differential studies of letter fluency found an AD-related advantage.[116,117] Rascovsky et al[117] matched autopsy-confirmed FTLD pathology with clinical records of pure FTD. They reported a significant double dissociation between group and generative fluency type, in which the FTD group had significantly worse outcomes on letter fluency and the AD group performed poorest on category relative to phonemic word fluency.

Attention and Executive Functioning

FTD is marked behaviorally by a prominent dysexecutive syndrome, and SD may also present with distinct behavioral dysfunction relatively early in the disease course; in contrast, behavioral disturbance often either is absent in PA or only appears as a late feature. Nevertheless, with some exceptions,[109,116,124,135,138,139] neuropsychologic measures of total achievement scores and reaction time do not differentiate between FTLDs/FTD and AD across tasks of attention, working memory, conceptualization/abstraction, mental flexibility, and set shifting, as well as maintenance[115,118-122,128,130,136,137] (studies on paradigms of attention and executive functioning within the FTLDs and between PA/SD and AD are few in overall number and are of equivocal outcome[98,107,108,115,118,119]). There are at least 2 broad reasons for this lack of differentiation. First, executive functions are mediated by frontal-subcortical and frontal connections with parietotemporal regions that are damaged in the FTLDs, as well as in Alzheimer's disease. Second, cognitive tests of executive functioning are multifactorial and preferentially tap dorsolateral frontal functioning,[140] which is diminished in AD and FTD. Error scores, on the other hand, might be a better gauge of ventromedial frontal dysfunction that is selective to FTD.[122] There is some emerging evidence that error scores are indeed elevated in FTD relative to AD, both associated with traditional measures of executive functioning[115,116,137] and across the disparate cognitive domains of language, spatial-perceptual functioning, and episodic learning.[118]

Episodic Memory

Diagnostic criteria for the FTLDs indicate that learning and memory are relatively preserved early in the disease course.[97] Although many studies have reported better learning scores in FTD as compared with AD,[42,109,115,116,120,122,127,129,130,133,135-139,141,142] no difference between groups on memory measures is a frequent outcome as well.[113,114,118,119,121,128,143] The nature of how memory and learning is affected in FTD likely accounts for these differences. FTD patients have difficulty effectively generating and implementing organized strategies to register and retrieve information.[141] As a result, measures of both recall and recognition are impaired regardless of the delay interval, but retention is significantly better as compared with the global anterograde amnesia of AD. FTD patients consistently outperform AD groups on measures of retention when retention is reported as a separate measure.[118,120,122,142] FTD patients also have been reported to perform better on acquisition trials in 1 study when learning was cued.[120] In addition, there is some evidence that FTD patients use less effectively organized recall (eg, greater serial clustering) as compared with AD.[141] Mixed results characterize differential memory performance across the FTLDs. A few studies have found equivalent verbal and visual memory between FTD, SD, and PA,[98,113,119] whereas others have noted worse verbal learning for SD as compared with FTD and PA.[108,114,115] Of note, no difference has been reported between Tau-positive and Tau-negative groups on verbal retention measures.[99]

Visual Information Processing

Similar to memory-related performance, the relative preservation of perceptual and spatial functioning is considered a supporting diagnostic feature for the FTLDs.[97] Although similar to evidence from memory studies, neuropsychologic findings are supportive of a spatial advantage associated with FTLDs/FTD as compared with AD in some studies,[118,122,124,127,129,130,133,144] but not in a sizable number of others.[107,114,116,117,121,131,137] Because the majority of spatial measures used require constructional ability (mostly figure copying), the measures employed confound spatial and perceptual ability with executive factors of organization, planning, and motor output. Examination of error score profiles on constructional tasks shows that patients with FTLDs/FTD make more executive-like errors, whereas AD patients make more spatially oriented

errors.[122,144] Additionally, FTD, SD, and PA groups do not appear to differ significantly on constructional measures.[98,108,110,123,131,138]

Behavioral/Psychiatric Symptoms

Given that FTD is largely diagnosed based on behavioral criteria, it is somewhat of a tautology to compare FTD with AD on defining features. Nonetheless, personality changes occur significantly more often among the FTLDs than in AD, although not all cases of FTD exhibit prominent changes in personality.[145] Also, as compared with AD, FTD is associated with higher levels of apathy, disinhibition, euphoria, and aberrant motor behavior.[129,137,138,146-148] Although there have been some attempts to divide FTD into apathetic and disinhibited subtypes, many FTD patients demonstrate both apathy and disinhibition.[149] FTD also is contrasted with AD by relatively greater emotional blunting and lack of empathy, poor personal hygiene, hyperorality (with an increased craving for carbohydrates and sweets in particular), and stereotyped behaviors.[150,151] Other psychiatric features, however, do not differ between FTD and AD, including delusions, hallucinations, depression, anxiety, agitation, and irritability.[128,138,146-148] Nevertheless, the depression observed in FTD is different than AD, as irritability/agitation without dysphoria or anhedonia is common. Results are mixed as to whether levels of aggression are similar between FTD and AD,[129,151] higher in FTD,[146] or higher in AD.[147] Although patients with PA appear to lack most of the behavioral features associated with FTD, SD patients show many similar behaviors.[146,149,152,153] SD is associated with similar levels of disinhibition, reduction in empathy, and stereotyped (particularly verbal) behaviors as in FTD, but SD patients show lower levels of apathy and more rigid and obsessive behaviors instead of unusual motor activity.[149]

CONCLUSIONS

With the use of appropriately sensitive measures in conjunction with examining patterns of results, significant differences emerge between the cognitive and behavioral profiles in AD and other neurodegenerative dementias. Preservation of dissociable mechanisms of episodic learning appears to be among the most useful discriminators between AD and the other dementias, including better verbal recall (immediate and delayed) in VCI/VaD, better contextual verbal delayed recall and recognition in DLB and PDD, and better multimodal retention in FTD. The presence of rapid forgetting, especially on verbal tasks, may suggest concomitant Alzheimer's disease even in the presence of considerable vascular pathology. Although clinical lore suggests that SD and PA variants of the FTLDs are associated with better visual learning and visual information processing as compared with AD, this proposed difference has not been verified empirically. Relative to AD, only VCI/VaD appears to be associated with worse executive performance on measures of reaction time and total achievement; however, worse performance on qualitative process measures of executive functioning differentiates the FTLDs (FTD and SD in particular) and the LBDs (DLB and PDD) from AD. The examination of fluctuating cognition in the LBDs with cognitive paradigms of attention appears to be promising. The LBDs are characterized by very defective visuoperceptual and spatial functioning as compared with AD, whereas AD does not differ appreciably from either VCI/VaD or FTD on perceptual/spatial measures; however, visual processing deficits in the latter disorders likely are secondary to executive functioning impairment. In the language domain, performance on measures of confrontation naming and verbal comprehension do not consistently differentiate AD from VCI/VaD, the LBDs, or FTD, although both PA and SD groups do show greater anomia and generalized aphasic deficits (expressive and receptive) as compared with AD and FTD. In contrast, differential performance on measures of generative word fluency may be useful in dissociating cognitive profiles between the dementias, especially in association with both antemortem and postmortem biological markers of disease-specific neurodegeneration. Pronounced psychomotor slowing appears to be a unique characteristic of VCI/VaD. When psychiatric disturbance is present, the neurodegenerative disorders tend to have distinct phenotypes: (1) paranoid delusions and mild affective disturbance in AD, (2) mood-congruent visual hallucinations in the LBDs, (3) poor comportment, disinhibition perhaps mixed with apathy, euphoria, and aberrant/stereotyped motor behavior in the FTLDs (with SD associated with greater behavioral disturbance as compared with PA), and (4) more significant affective dysfunction in VCI/VaD relative to AD.

Hopefully, this review helps to stimulate and direct further research necessary to define better the cognitive-behavioral profiles associated with the neurodegenerative dementias. Now that VCI/VaD, the LBDs, and the FTLDs have been contrasted with AD, it will be important to compare them with each other, including across different etiologies of VCI/VaD (intracranial vs extracranial), and other less common manifestations of the LBDs (multiple system atrophy) as well as the FTLDs (progressive supranuclear palsy, corticobasal degeneration). Subclinical versions of the LBDs and the FTLDs need to be defined, much like amnestic mild cognitive impairment for Alzheimer's disease and mild VCI relative to VaD. Disease-specific spectrum models of cognition and

behavior also should prove most helpful in advancing key current research issues, such as the development of dopaminergic and synuclein radioligands for the functional neuroimaging of the LBDs, and the burgeoning understanding of the genetics underlying the FTLDs. Finally, given the large degree of overlap between vascular, Alzheimer, and LB neuropathology among large autopsy series, it will be important to closely link the prospective use of appropriate standardized neuropsychological measures and experimental cognitive paradigms with retrospective pathology series to answer critical questions about how neurodegenerative comorbidities are expressed behaviorally.

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