

Cognitive Profiles Distinguishing Dementia Due to Alzheimer's Disease from Vascular and Lewy Body Dementia: A Literature Review

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Abstract

Introduction: Diagnosing the etiology underlying dementia symptoms can be difficult because of the broad nature of shared cognitive impairments across dementia subtypes. Therefore, we sought to differentiate the cognitive profiles of Alzheimer's disease (AD) from vascular dementia (VaD) and Lewy body dementia (LBD).

Methods: PubMed, ScienceDirect, Web of Science, Google Scholar, and PsychINFO were searched for studies comparing the cognitive profile of AD to those of VaD and LBD along the domains of memory, language, and executive function.

Results: Short-term and episodic memory were more severely impaired in AD than in VaD and LBD. Semantic memory was more impaired in AD than LBD, but it was similarly impaired in AD and VaD. Semantic fluency was worse in AD than in VaD, and phonemic fluency was worse in AD compared to VaD and LBD. Naming was more impaired in AD compared to VaD and LBD. Executive function impairments were similar or less severe in AD relative to VaD and LBD.

Discussion: Findings may be explained through neuropathological correlates of each disease. Tau proteins targeting the medial temporal lobes and synaptic loss in prefrontal cortices in AD may explain greater memory deficits in AD relative to VaD and LBD. In those with AD, the temporal lobes undergo greater atrophy than in those with VaD and LBD, possibly contributing to the greater semantic fluency impairments in AD. Greater white matter loss in frontal lobes in VaD may be a reason for a worse phonemic fluency in VaD relative to AD. Executive function impairments may be attributable to more deep white matter hyperintensities in those with VaD and more dopaminergic dysfunction of the basal ganglia in those with LBD relative to those with AD.

Conclusion: Understanding the cognitive profiles that differentiate AD from VaD and LBD would aid in more efficient and accurate diagnoses of dementia etiologies. Diagnoses could be further improved by using cognitive assessment in addition to neural and physiological measures. This knowledge may help identify individuals at risk of developing dementia, helping clinicians intervene early and prevent progression to severe stages.

Keywords: Alzheimer's disease; vascular dementia; Lewy body dementia; memory; language; executive function; executive functioning; attention

Introduction

As the proportion of older adults rises in many countries, so does the prevalence of dementia [1]. Dementia is a syndrome characterized by the progressive decline in cognitive abilities (such as memory, language, and executive function) to a degree that impacts one's ability to function independently [2]. The three most common causes of dementia are Alzheimer's disease (AD), vascular dementia (VaD) and Lewy body dementia (LBD) [3]. AD pathology is characterized by a loss of neurons and synapses [4], and this etiology accounts for up to 80% of all dementia cases [5]. This loss is due to the build-up of amyloid-beta (A β) proteins in the association areas of the brain and tau protein hyperphosphorylation in the medial temporal lobes and

association areas [5-6]. AD progresses in three stages: preclinical AD, mild cognitive impairment (MCI), and AD dementia [7].

VaD, the second most common cause of dementia [8], encompasses any vessel disorders that lead to cognitive decline. VaD can be divided into three subtypes: mixed dementia, in which AD and VaD both contribute to cognitive decline, post-stroke dementia, and subcortical VaD [9]. Unlike AD, VaD has no defining marker for its pathology, as the vascular changes found in VaD can also be found in healthy older adults [10].

LBD is a type of dementia characterized by cortical and subcortical build-up of α -synuclein proteins, which form Lewy bodies and A β and tau proteins [11-12]. Subtypes of

LBD, including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), share many clinical features, such as cognitive, motor, and neuropsychiatric symptoms [13-14]. These symptoms differ in onset times; in PDD, motor impairments precede cognitive decline [13-14], but the opposite pattern is seen in DLB [13,15]. Cognitive impairments are commonly seen in individuals with AD, VaD, and LBD. Therefore, it is important to distinguish between the three dementia etiologies, and this can be done using neuropsychological evaluations of the cognitive domains of memory, language, and executive function.

Memory is the ability to store and recall information [16], and can be measured by tasks such as the short-term memory (STM) binding task [17], in which participants study items and are tested in recall and recognition. Memory can be subdivided into implicit (i.e., outside our conscious awareness) and explicit (i.e., conscious) memory [18]. Explicit memory is further divided into episodic memory and semantic memory, which involve contextual recall of prior experience and recall of specific facts, respectively [19-20].

Studies examining language impairments in dementia have looked at oral verbal fluency as well as object naming. Verbal fluency, divided into phonemic and semantic fluency, involves retrieving information from memory [21-22] and is assessed based on the number of words generated in one minute [23]. Tests of phonemic fluency, such as the Controlled Oral Word Association Test (COWAT) [24], require participants to generate words that start with a given letter. Semantic fluency involves generation of words that fall under set categories [25], such as animals [26]. Word-retrieval impairments are commonly assessed using tasks such as the Boston Naming Test (BNT) [27] in which individuals name objects based on line drawings.

Executive function describes higher-order cognitive abilities that allow us to plan our actions, exhibit self-control, and adapt our behavior in unfamiliar situations [28-29]. Higher-order attention is an aspect of executive function that enables us to select and orient towards goal-related stimuli and regulate our responses accordingly [29-30]. The different subtypes, including sustained, selective, and divided attention, can be assessed using tasks such as the Test of Everyday Attention (TEA) [31]. Another aspect of executive function is inhibitory control, a measure of distractibility often assessed using the Stroop task [29]. Other common assessments of executive function include the Clock Drawing Test (CDT) and the Wisconsin Card Sorting Task (WCST) [32].

Older adults with VaD or LBD are often misdiagnosed with AD, leading to increased medical costs, which could be mitigated by an earlier and more informed diagnosis [33]. Varying degrees of cognitive deficits are commonly observed in different dementia subtypes. To help differentiate the cognitive profile of AD from those of VaD and LBD, this article aims to review the literature in neuropsychological performance that distinguishes these

dementia etiologies along the cognitive domains of memory, language, and executive function.

Methods

Five electronic databases (PubMed, ScienceDirect, Web of Science, Google Scholar, and PsychINFO) were searched for studies in which the cognitive profiles of AD, VaD and LBD were analyzed using neuropsychological tests. Search terms included "Alzheimer's disease", "Alzheimer's dementia", "vascular dementia", "Lewy body dementia", "Parkinson's disease dementia", "dementia with Lewy bodies", "memory" "explicit memory", "implicit memory", "short-term memory", "language", "semantic fluency", "verbal fluency", "executive function", "attention". The Boolean operators "and" and "or" were used to combine search terms. Inclusion criteria included (1) studies that compared AD to VaD or LBD along at least one of the three domains of interest using cognitive tests and (2) published between January 1990 and February 2020. Preprints were excluded. 41 studies were included in this review.

Results

Memory

Alzheimer's Disease and Vascular Dementia

AD showed a greater memory impairment overall compared to VaD. One study found that older adults with VaD and AD scored lower on the Benton Visual Retention Test compared to healthy controls (HCs) [34]. Individuals with AD were found to perform significantly worse than those with VaD on STM tasks, such as the recall memory task (RMT) [34], Prose Memory test, and the STM Binding task [17]. In another study, participants with VaD performed better on tests of episodic memory compared to individuals with AD, but not as well as HCs [34]. Similar degrees of impairment in semantic memory measured by the CDT [35] and other semantic memory tests [36-37] were observed in AD and VaD. No studies were found to have compared the differences in implicit and explicit memory between AD and VaD.

Alzheimer's Disease and Lewy Body Dementia

Overall, prior research has shown that memory is more impaired in AD than LBD. Individuals with AD were found to perform significantly worse on the temporary memory binding (TMB) task compared to PDD and HC groups [38]. Relative to individuals with AD, older adults with PDD performed better on STM tasks, including the RMT [39], the Prose Memory test, and the STM Binding task [17]. One study demonstrated that both AD and PDD groups showed similar levels of impairment on explicit memory tasks, such as the Bushchke Selective Reminding Test, relative to HCs [18]. Conversely, implicit memory was preserved in PDD [40] and AD, as measured using the Word-Stem Completion task and Maze Test [18]. Individuals with AD scored lower on the Five-Word Test, which measures episodic memory, compared to those with DLB [41]. Episodic memory

consolidation was observed to be more severely impaired in AD than DLB [42]. On measures of semantic memory, those with AD performed worse than those with PDD [43].

Language

Alzheimer's Disease and Vascular Dementia

Individuals with dementia often demonstrate language-related deficits, such as impaired phonemic fluency, semantic fluency, and naming [44]. There have been mixed findings on the verbal fluency impairments in AD and VaD. Semantic fluency was found to be more impaired in AD compared to VaD [45-46]. Some researchers [47-48] also found that individuals with VaD performed worse on phonemic fluency measures compared to those with AD, and HCs performed significantly better than the dementia groups. However, others found no significant differences in semantic [25,36,48-49] and phonemic fluency [25,45-46] between individuals with AD and those with VaD. On the BNT, a test of naming, many researchers found that individuals with AD performed worse than those with VaD [34,46,49-50]. As expected, HCs outperformed both dementia groups on the BNT. Individuals with AD were generally found to have worse semantic fluency than phonemic fluency, whereas those with VaD tended to be more impaired in phonemic fluency [45,47,51].

Alzheimer's Disease and Lewy Body Dementia

Studies investigating language impairments in LBD often distinguish DLB and PDD subtypes. Stern *et al.* [52] found that semantic fluency was less impaired in AD compared to PDD. However, most researchers found that semantic fluency is similarly impaired in AD compared to PDD [48,53-54] and DLB [22,26,55]. Phonemic fluency was found to be less impaired in AD relative to PDD [48] and DLB [26] as measured using the COWAT. Some researchers also found that participants with AD outperformed those with DLB [22,55] and PDD [52] on other phonemic fluency measures. However, others found that phonemic fluency was equally impaired in AD and PDD [53-54]. Individuals with AD were found to be more impaired than those with PDD [56] and DLB [57] on naming. Crowell *et al.* [26] found similar naming impairments in AD and DLB on the BNT.

Attention and Executive function

Alzheimer's Disease and Vascular Dementia

Studies comparing executive functioning in AD and VaD have found mixed results. On the TEA elevator counting task of sustained attention and Della Sala's dual task of divided attention, impairments were observed in VaD, but not in AD [58]. AD and VaD were found to be equally impaired in sustained attention measured using the digit vigilance task [31]. Selective attention, measured using the map search and elevator counting with distraction tasks of the TEA, was observed to be more impaired in VaD than in AD [58]. Using the CDT, some researchers have found comparable degrees of impairment in executive function in

both dementia groups [59-60], whereas others have found that individuals with AD outperformed those with VaD [35,61]. McGuinness *et al.* [31] found that both dementia groups were equally impaired on the Stroop task relative to HCs. However, Li *et al.* [62] found that individuals with VaD performed worse than individuals with AD on the Stroop task. Some studies have found similar impairments in the two dementia groups on the WCST relative to HCs [58,63], whereas others have found greater impairments in VaD than AD [64-65].

Alzheimer's Disease and Lewy Body Dementia

Older adults with AD have usually been found to outperform those with LBD on executive functioning tasks. On the TEA elevator counting task, individuals with AD performed as well as HCs, but those with DLB performed worse than the other two groups [66-67]. Comparable impairments in selective attention, as measured using the TEA elevator counting with distraction task, were found between AD and DLB [66-67]. In contrast, as measured by the map search task, selective attention was found to be more impaired in DLB than in AD [66-67]. Divided attention was comparable in AD relative to HCs, but it was impaired in DLB as measured using the Useful Field of View task [67] and Della Sala's dual task [66]. Calderon *et al.* [66] found that participants with AD performed significantly better than those with DLB on the Stroop task and the WCST. Park *et al.* [53] also found a lesser degree of impairment in individuals with AD relative to those with DLB using the Stroop task, whereas individuals with AD and PDD showed similar degrees of impairment. However, another study found no differences between AD and DLB groups on the Stroop task [68].

Discussion

Overall, studies suggested that episodic memory and STM were more impaired in AD than in LBD and VaD. Older adults with AD performed similarly to those with VaD on semantic memory tasks, but were more impaired compared to those with LBD. Implicit memory was found to be preserved in both LBD and AD. Semantic fluency was found to be similarly or more impaired in AD compared to VaD. Greater impairments in phonemic fluency were found in VaD relative to AD. Individuals with AD demonstrated similar impairments in semantic fluency, but less impairments in phonemic fluency relative to those with LBD. Naming was observed to be more impaired in AD compared to VaD and LBD. Although the results were mixed, the studies reviewed indicated that on average, VaD and LBD were associated with greater impairments relative to AD on measures of attention and executive function.

The findings of this review may be explained by the underlying neuropathology of each dementia subtype. Memory was found to be more severely impaired in individuals with AD compared to those with VaD and LBD. The greater deficits in episodic and semantic memory in AD

may be explained by the brain regions targeted by tau proteins. Specifically, these proteins target the medial temporal lobe regions, including the hippocampus [6,69-70]. Atrophy of the medial temporal lobe regions was also observed in VaD [71] and LBD [72], but to a greater extent in AD. The prefrontal cortex and sensory association areas involved in STM are affected in AD [4], which may explain the observed STM memory impairment.

Neuroimaging research provides insight into the different patterns of language impairments observed in dementia. Semantic fluency relies upon the temporal lobes, whereas phonemic fluency processes rely upon the frontal lobes [73]. Indeed, in their meta-analyses, Henry and Crawford [74] demonstrated that semantic fluency was more sensitive to temporal lobe lesions, and phonemic fluency was more sensitive to frontal lobe lesions. Similar levels of semantic fluency impairments have been seen in AD when compared to VaD and LBD. However, post-mortem magnetic resonance imaging (MRI) analysis showed higher medial temporal lobe atrophy in AD compared to VaD and LBD [72]. This MRI analysis does not explain the pattern of semantic fluency impairment observed in these dementia groups. Prior research has found more marked frontal lobe atrophy in LBD, supporting the finding of worse phonemic fluency in LBD compared to AD [75], but this finding was not supported by later research [76]. The neural mechanisms underlying naming have not been thoroughly investigated. Overall, the neuroimaging literature is inconclusive in differentiating between the three dementia etiologies. The inability of neuroimaging research alone to explain why different dementia etiologies lead to different patterns of impairments highlights the need for clinicians and researchers to use other physiological tests alongside neuroimaging. Future research should further investigate the neural underpinnings of verbal fluency and naming in the different dementia subtypes.

Impairments in executive function were demonstrated across three dementia groups, but the impairments were more substantial in VaD and LBD than in AD. The observed deficits may be due to the dopaminergic dysfunction of the basal ganglia in LBD [77] that is not seen in AD [78], as the basal ganglia have been shown to guide attention [79]. The greater executive function deficits seen in VaD compared to AD may be partially attributable to white matter hyperintensities (WMH), which are associated with impairments on fronto-executive tasks [80]. Deep WMH, which are found in deep white matter, are more frequently seen in VaD than in AD [81]. In summary, the consensus of the literature appears to indicate lower performance on executive functioning tasks in individuals with LBD and VaD relative to those with AD, which may be explained by the pathophysiology of the different dementia etiologies. Future studies could investigate the nature of the relationship between deep WMH and the different degrees of impairments of executive functions.

Identifying those who are at risk of developing dementia can help clinicians intervene early by beginning treatments and counseling. MCI, the stage between healthy aging and dementia, is characterized by some cognitive decline with relatively intact independent and occupational functioning [82]. Each of the reviewed dementia etiologies consists of prodromal MCI [83]. Clinical features, such as the severity of cognitive impairment and neuroimaging and fluid biomarkers, can predict the progression of MCI into AD dementia, but biomarkers for other MCI etiologies are less certain [82]. If the etiologies of MCI can be identified and symptoms are treated earlier, this could help prevent the onset of dementia, for which there are still no treatments available [84].

To maximize the efficiency and accuracy of AD, LBD, and VaD diagnoses, physiological and neuroimaging tests can be used in addition to neuropsychological tests. For example, cerebrospinal fluid concentrations of total tau protein, phosphorylated tau protein, and A β 1-42, can be combined to yield a classification accuracy above 85% between VaD, AD, and mixed dementia [85], as well as a sensitivity of 90% between LBD and AD [86]. Additionally, electroencephalography (EEG) has also been shown to be useful in discriminating between dementia etiologies [87]. A combined EEG and MRI model would also aid in differentiating AD from other dementia subtypes, as this method yielded a 90% classification accuracy between AD and DLB [88]. Combining cognitive assessments, physiological measures, and neuroimaging would allow for earlier, more accurate diagnoses of dementia subtypes, which could lead to more efficient development of interventions.

Differences in exclusion criteria varied across the studies we reviewed, which could affect the generalizability of our results. Although most studies used the consensus criteria for diagnosis of AD, VaD, and LBD [46], the exclusion criteria were not always uniform. Many authors excluded participants with psychotic disorders, history of substance abuse, and concurrent medication use [22,45,53], but not all authors confirmed the absence of vascular damage in participants with AD or LBD [39,47,49]. Therefore, some studies may have unknowingly included participants with mixed dementia instead of those with “pure” AD, VaD, or LBD. The variation in exclusion criteria could contribute to the lack of uniformity of the findings reviewed.

Future studies could consider comparing AD with other forms of dementia not reviewed in the present study (such as frontotemporal dementia) as well as mixed dementia. Additionally, other domains, such as visuospatial, logical reasoning, and psychiatric symptoms could also be compared between different dementia etiologies to provide a better understanding and diagnosis of neurodegenerative diseases.

Conclusions

Cases of dementia will continue to rise as the population of older adults increases. Distinguishing between the cognitive profiles of different dementia subtypes, as done in this review, may allow for better understanding and management of dementia symptoms. Although some clear differences between AD, VaD, and LBD along the three domains of interest have been identified, there are many discrepancies between studies regarding the degrees of impairments in these subtypes. Therefore, to increase diagnostic efficiency and accuracy, cognitive assessments should be used in conjunction with neural and physiological tests.

List of Abbreviations Used

AD: Alzheimer's disease
VaD: vascular dementia
LBD: Lewy body dementia
A β : amyloid-beta
MCI: mild cognitive impairment
PDD: Parkinson's disease dementia
DLB: dementia with Lewy bodies
STM: short-term memory
COWAT: controlled oral word association test
BNT: Boston naming test
TEA: test of everyday attention
CDT: clock drawing test
WCST: Wisconsin card sorting task
HC: healthy control
RMT: recall memory task
TMB: temporary memory binding
MRI: magnetic resonance imaging
WMH: white matter hyperintensities
EEG: electroencephalography

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

Our study did not require ethics approval or participant consent as we conducted a review of the literature.

Authors' Contributions

MOB: Made substantial contributions to the drafting of the manuscript, revised the manuscript critically, and gave final approval of the version to be published.

AAS: Made substantial contributions to the drafting of the manuscript, revised the manuscript critically, and gave final approval of the version to be published.

HYP: Made substantial contributions to the drafting of the manuscript, revised the manuscript critically, and gave final approval of the version to be published.

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