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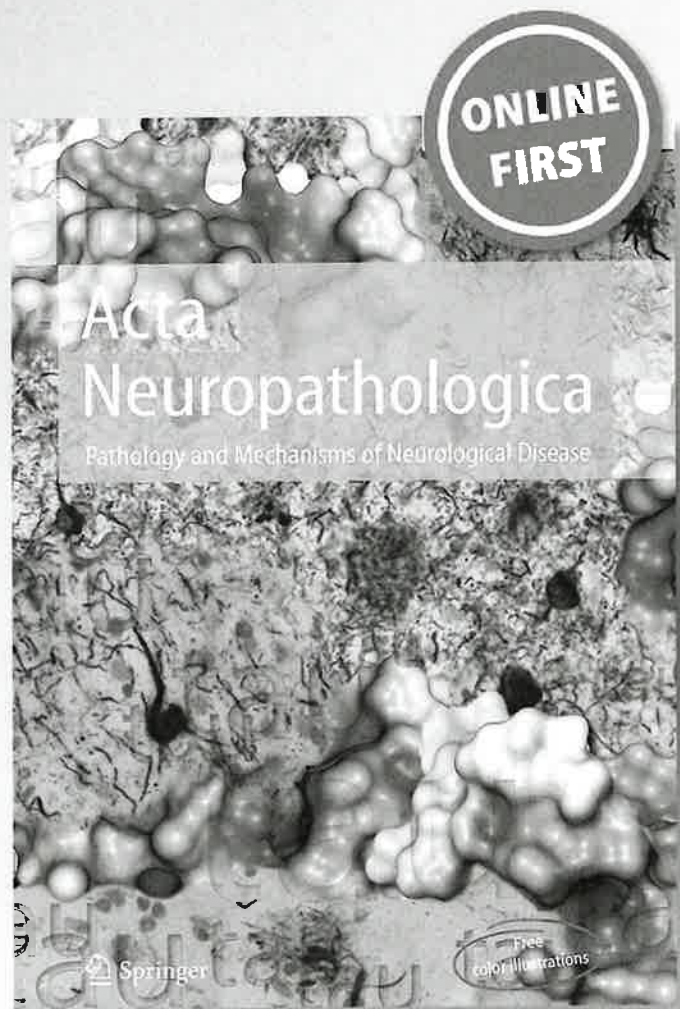
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REVIEW

Impact of multiple pathologies on the threshold for clinically overt dementia

Alifiya Kapasi[1,3] · Charles DeCarli[2] · Julie A. Schneider[1,3,4]

Abstract Longitudinal clinical–pathological studies have increasingly recognized the importance of mixed pathologies (the coexistence of one or more neurodegenerative and cerebrovascular disease pathologies) as important factors in the development of Alzheimer's disease (AD) and other forms of dementia. Older persons with AD pathology, often have concomitant cerebrovascular disease pathologies (macroinfarcts, microinfarcts, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy) as well as other concomitant neurodegenerative disease pathologies (Lewy bodies, TDP-43, hippocampal sclerosis). These additional pathologies lower the threshold for clinical diagnosis of AD. Many of these findings from pathologic studies, especially for CVD, have been confirmed using sophisticated neuroimaging technologies. In vivo biomarker studies are necessary to provide an understanding of specific pathologic contributions and time course relationships along the spectrum of accumulating pathologies. In this review, we provide a clinical–pathological perspective on the role of multiple brain pathologies in dementia followed by a review of the available clinical and biomarker data on some of the mixed pathologies.

Introduction

The most common causes of dementia in old age are Alzheimer's disease (AD), cerebrovascular disease (CVD), and Lewy body disease (LBD). There is also increasing recognition for the role of TAR DNA-binding protein 43 (TDP-43) and hippocampal sclerosis (HS) pathology, especially in the oldest old [81, 94], but these pathologies are not mutually exclusive. Indeed, multiple studies now show that a large proportion of older persons harbor multiple types of pathologies in their brain. The nomenclature for this phenomenon has been variably referred to several terms including multimorbidity [57], mixed pathologies [112], multiple pathologies [64], and neuropathologic comorbidity, [138]. These mixed pathologies are not only present in persons with dementia but also in those diagnosed specifically with AD dementia. While most persons with AD dementia are confirmed to have a pathologic diagnosis of AD, additional vascular and neurodegenerative pathologies are found in most cases [56].

The clinical counterpart to mixed pathologies is "mixed dementia," however, this term is often used to denote the presence of AD with vascular pathology (and specifically infarcts or white matter changes), whereas the spectrum of mixed pathologies goes well beyond infarcts to include other vascular pathologies (microinfarcts and vessel diseases) and non-AD degenerative pathologies (Lewy bodies, TDP-43, and HS). Unfortunately, because of lack of good biomarkers, and overlapping cognitive phenotypes, there are few guidelines for a diagnosis of mixed versus single pathology dementias.

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Converging evidence from multiple longitudinal study cohorts (Table 1) have set the benchmark for providing evidence to indicate that the pathophysiologic process of AD dementia may be a cumulative result of neurodegenerative and vascular pathologies [2, 58, 110, 138]. There is some evidence that the neurodegenerative pathologies may account for a larger percentage of the variability of cognitive decline in aging [16]. However, it is important to note that there still can be considerable difficulty determining the relative impact of differing pathological lesions on a single person's cognition, given the variability in baseline cognition, lack of biomarkers, and pathologic distributions and severities that may be difficult to ascertain during life. In addition, from a public health standpoint the high prevalence of vascular disease may make it a more desirable target for intervention. Indeed, there is some evidence that reduction in vascular risk factors may be related to a declining incidence of dementia [108]. Interpreting the literature of mixed pathologies can also be difficult due to considerable variations in demographics, study design, and neuropathological assessments between different cohorts.

The literature raises some important questions: Which specific CVD and neurodegenerative pathologies lower the cognitive threshold to develop AD dementia? Do specific pathologies interact to potentiate AD, other neurodegenerative, or vascular specific pathways? With the coexistence of multiple pathologies, which pathologies are driving the neurodegenerative process?

In this review, we will discuss the clinical and pathological evidence and implications of multiple brain pathologies in aging and dementia. We will start with the post-mortem studies that have provided much of the groundwork in the field of mixed brain pathologies; followed by a clinical perspective on the interpretation of pathologic studies; and a summary of clinical evidence for the influence of mixed pathologies on cognition and dementia. We conclude by summarizing the current state of the literature and recommendations for future directions.

Mixed vascular and AD pathologies

In recent years, the role of mixed vascular and AD pathologies in the pathogenesis of cognitive impairment and dementia has received considerable interest. Several large longitudinal cohort studies have investigated the coexistence of CVD with AD pathology in persons with dementia, with some showing an additive relationship and others showing a synergistic contribution to cognitive impairment (mixed dementia) [35, 97, 116, 119]. The spectrum of vascular brain injury (VBI) assessed by neuropathology includes large macroscopic, lacunar, and microscopic infarcts, hemorrhages, and vessel pathologies including cerebral amyloid angiopathy, intracranial atherosclerosis, and arteriolosclerosis.

Data from the ROS/MAP cohort showed about 50% of persons diagnosed with probable AD had mixed pathologies (AD, PD/LBD, or macroscopic infarcts), of which the most common is the presence of AD pathology and infarcts at 38% [111]. However, this study is an underestimate of mixed AD and vascular pathology since it did not take into account microinfarcts or any of the vessel diseases which are also commonly present in addition to AD, and shown to contribute to cognitive impairment. Indeed, updated data from ROS/MAP presented in the current review (see Table 2) shows that almost 75% of persons with a pathologic diagnosis have one or more of the stated vascular pathologies. Several studies indicate the presence of multiple macroscopic infarcts has more effect with cognitive impairment than the size of a single infarct [114, 125, 137], however, the proposal of size could be argued as microinfarcts have also been shown to be powerful determinants of

Table 1 Overview of the community-based cohorts discussed in this review

Cohort	Country	Study design	Initiated	References
Religious orders study (ROS)	USA	Catholic nuns, priests, and brothers (community cohort)	1993	[12]
Memory and aging project (MAP)	USA	Older persons without known dementia (community cohort)	1997	[13]
The nun study	USA	Catholic sisters with and without dementia (birth cohort)	1986	[119]
Honolulu Asian Aging study (HAAS)	USA	Japanese–American men (population study)	1991	[137]
The 90+ study	USA	Older persons ≥90 years (cohort study)	2003	[24]
Adult changes in thought (ACT)	USA	Older persons ≥65 years (population study)	1994	[20]
Vantaa 85+	Finland	Older persons ≥85 years (population study)	1991	[124]
Medical research council cognitive function in aging study	UK	General population-based cohort ≥65 years	1989	[97]
Baltimore longitudinal study of aging	USA	Persons ≥20 years (cohort study)	1958	[125]

Table 2 Prevalence of mixed pathologies in ROS/MAP

Pathology	Clinical diagnosis		
	No cognitive impairment ($n = 360$)	Mild cognitive impairment ($n = 271$)	Probable AD ($n = 447$)
No vascular* or other degenerative**	50 (13.89%)	12 (4.43%)	4 (0.89%)
Vascular only	102 (28.33%)	57 (21.03%)	22 (4.92%)
Other degenerative only (no AD)	14 (3.89%)	8 (2.95%)	6 (1.34%)
Other degenerative (no AD) + vascular	41 (11.39%)	28 (10.33%)	35 (7.83%)
AD only	30 (8.33%)	20 (7.38%)	14 (3.13%)
AD + vascular	75 (20.83%)	65 (23.99%)	122 (27.29%)
AD + other degenerative	6 (1.67%)	17 (6.27%)	34 (7.61%)
AD + other degenerative + vascular	42 (11.67%)	64 (23.62%)	210 (46.98%)

* vascular includes macroinfarcts or microinfarcts, or moderate to severe atherosclerosis, arteriolosclerosis, or cerebral amyloid angiopathy

** other degenerative includes Lewy body, TDP-43, and hippocampal sclerosis pathology only

dementia [4, 125], although when considering macro- and microinfarcts, size, number, and location are all important. There was some suggestion of an interaction between AD and vascular pathology in the Nun study. Specifically, only those participants with a pathologic diagnosis of AD and 1 or 2 lacunar infarcts showed higher prevalence of dementia, thus prevalent clinical dementia was crucial upon whether there were lacunar infarcts in the basal ganglia, thalamus, and deep white matter [119]. Studies including the MAP cohort also documented subcortical infarcts as important correlates of cognitive impairment and dementia, however, the effects were additive rather than synergistic [114]. The Baltimore Longitudinal Study of Aging documented 35% of persons with AD pathology and hemispheral infarcts, and suggests only the hemispheral infarcts drive the effect with dementia. However, their definition of hemispheral infarcts included infarcts other studies described as subcortical [125].

Microinfarcts are increasingly recognized in large community-based cohorts [4, 50, 75, 112, 120] and in persons older than 90, the oldest old [25]. Estimates of microinfarct prevalence in the elderly range from 16% to 46% [4, 50, 75, 112, 122], and jump to 51% in the oldest old [25]. Indeed, microinfarcts are also highly prevalent in persons with probable AD, vascular dementia, and mixed dementia [19, 43, 130]. Microinfarcts commonly coexist with other pathologies including AD pathology and macroscopic infarcts. For this reason, statistical models adjusting for these pathologies are required to assess whether microinfarcts have an independent contribution to cognitive decline or dementia. Using these statistical approaches, multiple studies have shown microinfarcts have an independent contribution to cognitive decline or dementia. In particular, the relationship with dementia appears to be driven by the presence of cortical microinfarcts [25, 50] and in multiple studies only the presence of multiple cortical microinfarcts

contributed to dementia [4, 120], highlighting the importance of the number and location of lesions. To enhance understanding on how microinfarcts influence cognitive function, studies have targeted examination for specific domains. In the ROS cohort microinfarcts were associated with lower episodic memory, perceptual speed, and semantic memory [4], whereas in the stroke registry investigating cognitive decline (STRIDE) study microinfarcts were associated with lower visuospatial abilities [133]. Differences in these findings are most likely due to the different methodology for examination of microinfarcts. Identification of microinfarcts in the ROS study utilized routine histologic methods, whereas the method of detection in the STRIDE cohort used neuroimaging which as noted below only detects the largest of cortical microinfarcts. Further differences include age, death/autopsy, and the assessment and scoring for cognitive impairment.

Clinico-pathological studies have provided vast insights into microinfarct pathology and their contribution to cognition or dementia. However, autopsy studies are cross-sectional and due to sampling limitations, may underestimate the burden of microinfarcts. Using an eloquent estimation method, a study showed the presence of 1 or 2 microinfarcts implies an estimated burden of hundreds of microinfarcts in the brain [136]. Studies employing sophisticated neuroimaging techniques have also provided a promising approach to investigate the burden of microinfarct pathology during life [9, 74, 126]. However, the size of many microinfarcts is below the limit of conventional imaging techniques, rendering them to be typically examined by traditional neuropathology methods.

Vessel pathologies, including cerebral amyloid angiopathy (CAA), arteriolosclerosis, and atherosclerosis are very common mixed pathologies in aging, especially with AD pathology, and have been shown to contribute to cognitive impairment in late life even after controlling for AD

and infarct pathology [5, 17]. Sporadic CAA, which is very commonly associated with AD pathology in aging, has been shown to be independently associated with an increase in the odds of a diagnosis of clinical AD, dementia [17], lower late-life cognition [103], and an increased trajectory of cognitive decline [17]. In the ROS/MAP cohort, CAA was associated with lower function in multiple cognitive domains including episodic memory, the clinical hallmark of AD [6]. An autopsy study using data from the Rochester epidemiology project reported CAA to be higher in patients with mixed dementia compared to "pure" AD and vascular dementia [28]. In the HAAS study, the presence of CAA in one neocortical region was present in 44% of persons and associated with higher means of AD pathology and the presence of 1 APOE-ε4allele [103]. CAA-associated pathologies such as lobar intracerebral hemorrhages, microinfarcts or microbleeds are often found in persons with dementia and cognitive impairment [2]. While tissue loss is one mechanism by which CAA is likely related to impaired cognition, studies suggest that CAA is also related to cognitive impairment separate from at least some of these lesions [16].

Arteriolosclerosis (intraparenchymal small vessel disease also called lipohyalinosis) is also common and has been shown to be independently associated with poorer global cognitive function and increased odds for developing clinical AD and dementia [3, 49]. In an effort to understand involvement of cerebrovascular disease with late-life cognitive trajectories, a recent study used a large autopsy cohort of over 2000 subjects compiled from six different centers. Data from the study showed the odds of having a poorer trajectory for verbal reasoning was doubled with the presence of severe arteriolosclerosis [73]. In the ROS/MAP cohort, significant arteriolosclerosis and intracranial atherosclerosis were also found to be associated with global cognitive dysfunction, specifically in cognitive domains including episodic memory, semantic memory, perceptual speed, and visuospatial abilities [3]. The impact of these vessel diseases was independent of other neurodegenerative and vascular pathologies including infarcts.

The pathogenesis of cognitive decline in persons with vessel disease is poorly understood. Vessel disease has been correlated with white matter pathology, volumetric changes [26], as well as inflammatory and blood brain barrier changes. The role of vascular pathology is likely to be a growing public health problem since mixed AD and vascular pathology continues to rise in the oldest old [56]. It is also likely to be an important issue in community dwelling African American and potentially other minorities. Black clinic participants had more severe arteriolosclerosis and atherosclerosis than white participants [11]. One possible explanation for this may be higher prevalence for diabetes and hypertension, conditions associated with vessel

disease [11]. Vascular pathologies have been associated with AD-related pathological changes in the south Asian aging population, of which small vessel lesions showed a higher degree of association [140]. Overall, the literature suggests that vascular pathologies mixed with AD pathology are very common. While some studies suggest vascular pathologies directly add to the likelihood of clinical AD, others suggest there is a synergistic effect between AD and vascular pathologies [75]. Mechanisms of vascular cognitive impairment and the contribution of vascular pathologies to AD pathology remains an area of intense research efforts. Common risk factors, interactions, and mechanisms of injury from AD and vascular pathologies also remain topics of great interest.

Mixed Lewy body and AD pathologies

Other common pathologies presented in persons with mixed pathologies are Lewy bodies [7, 131]. Lewy bodies are intraneuronal aggregates of α-synuclein protein. They are common in the aging brain and often co-occur with AD pathology in the brains of older people. In the ROS/MAP cohort, over 60% of participants with Lewy body pathology had a pathologic diagnosis of AD [115]. Mixed AD and LB pathologies are commonly observed in black and white persons, however, there are some racial differences underlying the mixed pathology profile. Overall, black clinic participants were more likely to have mixed pathology. Compared to white persons, mixed AD with Lewy body pathology was the most prevalent in black patients [11]. The authors hypothesize that this increase in prevalence could be the result of selection bias from a clinic study. Of note, a higher prevalence of LB pathology in whites has also been previously observed in community-based vs. clinic-based cohorts. This has been hypothesized to be related to the association of LB pathology with behavioral, sleep, and movement issues, making families more likely to bring their relative into a tertiary care setting for an evaluation [113]. Indeed, in a study combining multiple cohorts from differing settings, the clinical diagnosis of Dementia with Lewy body disease (Lewy body dementia or Parkinson's disease) did not differ between races [42]. One needs to be cautious inferring prevalence of subtypes of dementia using clinic samples.

Although Lewy body pathology alone can be associated with cognitive impairment and dementia, it is now commonly recognized that Lewy body pathology in aging occurs most in conjunction with a pathologic diagnosis of AD. In the presence of AD pathology, most studies suggest the relationship between the pathologies is additive [46, 72], nonetheless, Lewy bodies have been associated with faster decline in most, but not all studies [132].

Regionalization of Lewy body burden in the brain may affect the relationship with cognition. The distribution of Lewy body pathology has been described to follow a caudal to rostral progression, from the nigra to limbic regions to the neocortex, giving rise to nigra-predominant, limbic-type, and neocortical-type classifications. Amygdala predominant disease may reflect an alternate progression of LB pathology. While it is commonly proposed that neocortical and limbic Lewy body pathology are central in determining cognitive impairment and dementia [115, 120], others have challenged this to suggest Lewy body pathology in the brainstem may also be important correlates of cognitive impairment [65]; however, this finding is not replicated in all studies [115]. Some propose the importance of AD pathology burden, and suggest neocortical Lewy body pathology is not sufficient to cause severe global cognitive impairment and that AD pathology must be present, reflecting a synergistic relationship [92]. Other studies suggest that specifically burden of neurofibrillary tangles (NFTs) play a central role in pathogenesis in patients with Lewy body spectrum disorders, as increasing levels of NFT burden showed worsening of prognosis in these patients. Indeed, increasing levels of AD pathology in these patients also showed an increasing burden of α-synuclein pathology [51]. Interestingly, in the Vantaa85 + study clinical features of DLB correlated highly with neurofibrillary staging rather than neocortical Lewy body pathology [100], which may reflect differences in the underlying neuropathological basis of dementia in the oldest old, persons older than 85 or 90 [124]. Other studies have also highlighted differences with increasing age [55]. Analyses from the MRC-CFAS and the MAP/ROS cohort also showed decreasing association between AD pathology and clinical dementia with increasing age [55, 109].

Mixed TDP-43, AD, and hippocampal sclerosis pathology

TDP-43 pathology is commonly observed with AD pathology and HS, and is an important factor contributing to cognitive decline and dementia in late life. TDP-43 is related to lower episodic memory in persons without AD or HS pathology [90]. Stereotypical deposition of TDP-43 in aging and AD has previously been reported, with the amygdala being the most common region for TDP-43 burden [142], followed sequentially by the entorhinal cortex, hippocampus, and inferior or middle temporal cortex, suggesting a gradual progression over time. Final involvement may include the mid-frontal cortex [56] and basal ganglia [59].

Concomitant TDP-43 pathology plays an important role in modifying clinical and radiological AD phenotype.

Subjects with AD pathology and TDP-43 inclusions were ten times more likely to be cognitively impaired than subjects without TDP-43 [61]. Specifically, when controlling for HS and AD pathology, TDP-43 pathology is associated with episodic memory impairment [61]. TDP-43 may also have independent effects on neuroimaging features associated with AD. Indeed, MRI imaging studies show greater hippocampal atrophy with greater TDP-43 burden [60]. TDP-43 is associated with HS, tangle density, and amyloid burden, but not the pathologies of macroinfarcts, microinfarcts and Lewy bodies. The presence of TDP-43 pathology independently increases the trajectory of cognitive decline [142], and when with HS [91] and/or AD pathology it increases the odds of developing dementia [56]. However, TDP-43 is not exclusively found in AD cases, but also observed in mixed AD/LB and DLB cases. Prevalence of TDP-43 pathology was higher in AD dementia cases at 74%, followed by mixed AD/DLB at 53% [81]. In ROS/MAP subjects with a clinical diagnosis of AD, TDP-43 was found in 64% of subjects and reduced the number of persons with "pure" AD pathology to less than 10%. In the same study, it was reported that when TDP-43 extends from the amygdala to or beyond the hippocampus, it significantly increases the odds of dementia over and beyond the AD pathology [56]. Interestingly, elevated TDP-43 profiles were observed in persons who developed dementia and not in persons with mild-cognitive impairment [142], suggesting importance of TDP-43 towards the progression of dementia rather than the onset of cognitive impairment.

The pathogenesis in which TDP-43 contributes to cognitive impairment still remains unknown. TDP-43 is related to neuronal loss, which may arise due to deleterious loss of TDP-43 from the nucleus [76]. Interestingly, a study investigating pathological correlates in a cohort of ALS patients show TDP-43 and microglial activation, a feature commonly associated with neuronal loss, are highly correlated with cognitive impairment, specifically with executive function. However, they did not correlate with MMSE [21]. These findings emphasize the need for increased research to further understand the pathophysiological mechanisms underlying TDP-43 pathology.

HS is defined by significant neuronal loss and gliosis in the CA1 and/or the subiculum regions of the hippocampus. HS is increasingly being recognized in persons with dementia, specifically persons with AD dementia and frontal lobar degeneration (FTD) [33]. TDP-43 pathology was seen in almost 90% of cases with HS [95]. HS is twice as common in older persons >90 than in younger persons and also commonly coexists with AD pathology and Lewy body pathology. However, in a model controlling for age, AD, Lewy body, and TDP-43, only TDP-43 had a significant relationship with HS. TDP-43 in the absence of HS is

associated with episodic memory loss; together HS with TDP-43 is associated with lower function in multiple cognitive domains [91]. Finally, in persons without a pathologic diagnosis of AD, TDP-43 is an important factor in episodic memory impairment [90]. Another etiological mechanism that may contribute to the pathogenesis of HS is ischemic injury, suggesting involvement of cerebrovascular disease [45, 95]. Indeed, it is well known in the neuropathology literature that global hypoxic/ischemic injury can result in severe damage to CA1/subiculum of the hippocampus. Support, for vascular etiologic factors, comes from data from multiple large autopsy series investigating the association between cerebrovascular pathology and HS-aging showing a strong association of arteriolosclerosis in the frontal cortex with HS. Other vascular pathologies and vascular risk factors were not associated [94, 96]. Despite recent advances in the literature regarding HS-Aging, a term to describe hippocampal sclerosis of aging, definitive characterization of clinical and pathological features still remains unclear. A recent approach to better characterize this process has been through genetic–phenotype correlations. Previous studies have been linked HS-Aging to single nucleotide polymorphisms (SNPs) within four genes; GRN, TMEM106B, ABCC9, and KCNMB2. Further studies show these SNPs are associated with distinct pattern of cortical atrophy in the frontal lobes [98].

Mixed pathologies: update from the religious orders study and rush memory and aging project

Here we update the prevalence and proportions of mixed pathologies we have gathered from the ROS/MAP studies (general information on these community-based cohorts and clinical and pathologic diagnoses can be found in [12, 13]. We included 1078 consecutive deceased and autopsied subjects (mean age of death, 89 years, SD = 6.5; 32% men; mean education, 16 years, SD = 3.6) since 1993 that had completed clinical diagnosis proximate to death (no cognitive impairment (NCI),

mild cognitive impairment (MCI) or probable AD) and completed pathologic assessments for AD (NIA-Reagan criteria intermediate or high), infarcts (chronic macro or micro), vessel disease (moderate or severe atherosclerosis, arteriolosclerosis, or CAA), TDP-43 pathology advanced to hippocampus or beyond, cortical LB disease, and the presence of hippocampal sclerosis. Each of these pathologies has been previously shown to lower the threshold for cognitive impairment. The prevalence of these pathologies across each diagnostic group is shown in Fig. 1 and Table 2. As previously described [1,2], a pathologic diagnosis of AD is common in older persons who die without cognitive impairment, is seen in about half of those with MCI, and confirmed in majority (85%) of older persons with a clinical diagnosis of probable AD. However, these new data that now include additional degenerative (LB, TDP, HS) and vascular pathologies (microinfarcts, moderate to severe atherosclerosis, arteriolosclerosis and CAA) known to contribute to the odds of cognitive impairment or dementia, now demonstrate that over 85% of those with MCI, and over 95% of those with probable AD have mixed pathologies. A striking aspect of these updated numbers and figure is the proportion of persons with a pathologic diagnosis of AD and both vascular and other degenerative pathologies shifting from 11% in subjects with NCI, to 24% in subjects with MCI, to 47% in subjects with probable AD. In persons with probable AD and mixed AD pathology, vascular disease is present in approximately 90% and other degenerative diseases in about 65% (Table 2). Mixed AD with vessel disease and infarcts is the most common of mixed AD/vascular pathologies (present in about 50% of persons with AD), whereas mixed AD with TDP-43 is the most common of the mixed AD/other degenerative pathologies (Fig. 2a). In those with probable AD without a pathologic diagnosis of AD, mixed vascular disease and other degenerative diseases are also very common. Infarcts with moderate to severe vessel disease remains the most common of the vascular pathologies, whereas TDP-43/HS is more prevalent than TDP-43 without HS (Fig. 2b).

Fig. 1 Mixed pathologies in ROS/MAP. Prevalence of mixed pathologies in ROS/MAP subjects with a clinical diagnosis of no cognitive impairment, mild cognitive impairment, and probable AD. *V* vascular, *OD* other degenerative, *AD* Alzheimer's disease, *0* no vascular or neurodegenerative pathology described in Table 2
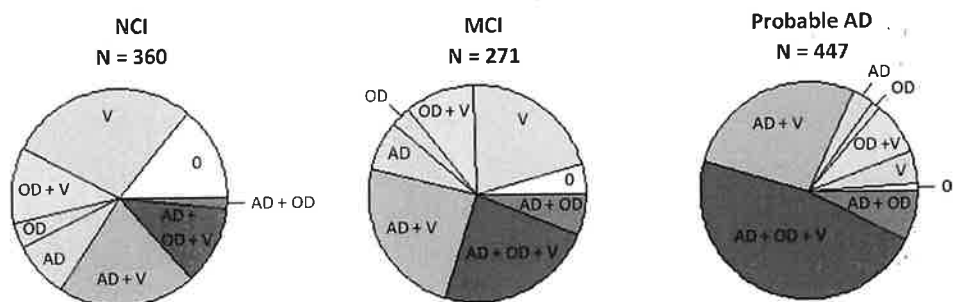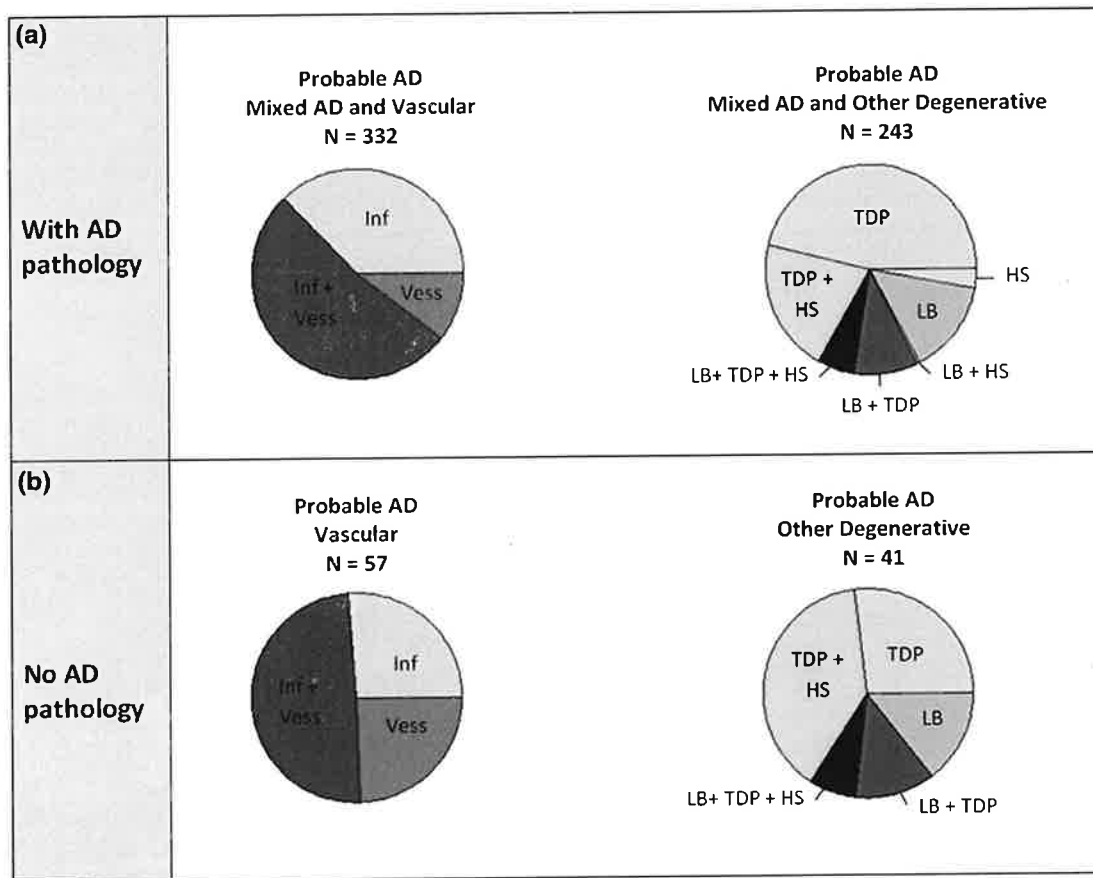
Fig. 2 Prevalence of mixed pathologies in ROS/MAP subjects with probable AD. Prevalence of mixed AD pathology in ROS/MAP subjects with probable AD and with a pathologic diagnosis of AD (a). Prevalence of vascular and other degenerative pathologies in ROS/MAP subjects with probable AD, without a pathological diagnosis of AD (b). *inf* infarcts (including macro- and microinfarcts), *Vess* vessel disease (including arteriolosclerosis, CAA, and atherosclerosis), *TDP* Tar DNA-binding protein 43, *HS* hippocampal sclerosis, *LB* Lewy body

Overview of mixed pathologies

Overall, a large body of data suggests that mixed pathologies, most commonly AD pathology with vascular or other degenerative pathologies, are very common in aging and that these mixed pathologies are important in lowering the threshold for cognitive impairment and dementia. There is some evidence that the neurodegenerative pathologies are more potent than the vascular; however, the latter may be more common and numerous. Despite different methodologies clinical and neuropathological assessments in large clinical-pathologic studies almost all studies have shown common mixed pathologies and an additive or synergistic role of additional pathologies, with lowering of the threshold for the diagnosis of dementia.

There remain many questions. The extent to which each of these pathologies independently and together contributes to the pathophysiologic processes underlying neurodegeneration and cognitive decline is unclear. Each pathology may contribute differentially to specific cognitive domains [3, 4, 6, 91, 114, 115, 142] and decline [16, 141] and may affect baselines as well as trajectories [18, 141]. Indeed, not only is the number of pathologies that is important, but the type of pathologies that coexist [64]. It is also important to recognize that these pathologic brain markers do not tell the whole story. Data from a longitudinal clinical–pathological study showed combining global AD pathology, plaques, tangles, macroscopic infarcts, microscopic infarcts, and Lewy body pathologies only accounted for 41% of the variation of cognitive decline, leaving about 60% of the variance of cognitive decline unexplained. While this study did not account for the pathologies of hippocampal sclerosis, TDP-43 pathology, and small vessel disease, all of which have been associated with cognitive impairment [16], it does raise more questions regarding the other potential links between brain pathologies, reserve factors, and cognitive decline.

The pathologic literature suggests both vascular and neurodegenerative pathologies lower cognitive threshold, however, that the timing of decline may vary by pathology [141, 148]. For example, infarct pathology has been shown to be associated with early cognitive decline, while Lewy body pathology is associated with terminal cognitive decline. Assessing the temporal course of neurodegenerative pathologies including neurofibrillary tangles, Lewy bodies, TDP-43, and hippocampal sclerosis showed a differential relationship with cognition, with very high TDP-43 potently affecting incipient cognitive decline [141, 148]. Clinical progression to dementia can also vary depending on the combination of pathologies vs. presence of single pathology. Data from the U.S. Alzheimer's Disease Center show persons with mixed AD/LBD pathology showed a faster progression to clinical dementia than persons with AD/VBI or AD alone. Subsequent analyses showed additional pathologies with intermediate levels of AD pathology having a higher progression rate than pathologies with high levels of AD pathology, suggesting impact of mixed pathologies may be dependent on the burden of AD pathology [20].

Many studies have relied on subjective interpretation to characterize pathology measures, and whilst this approach has advanced the literature in understanding the role of mixed pathologies with cognition, there are limitations, and more objective and quantitative measures are warranted. Stereology methods have been important in computerized image analysis; further advances in technology have been made to promote digital neuropathological assessments [96]. Finally, in some epidemiologic clinical-pathologic studies, sophisticated statistical modeling can be used to query trajectories and stages of cognitive decline in relation to pathology. However, the pathology is defined as cross-sectional and the observed effect is the cumulative burden of pathologies. This poses an increasing need to better understand the burden of vascular and neurodegenerative pathologies during life.

The concept of dementia with mixed pathologies: a perspective on pathology

Dementia is a clinical syndrome associated with both cognitive and functional deficits [8]. Clinicians traditionally ascribe a specific etiology to the dementia syndrome for the obvious purpose of prognosis and management [40, 83, 84, 104, 107]. More recent definitions of dementia have evolved to recognize that "Dementia is a syndrome, an overlapping constellation of signs and symptoms of impaired cognition caused by multiple disorders, which can be difficult to distinguish clinically" [86]. This new conceptual approach to dementia pathophysiology acknowledges that many individuals with dementia suffer from multiple pathologies, particularly when assessing non-select community-based populations [8, 112, 138] or the oldest old [25]. Consequently, newer diagnostic assessments have expanded to indicate a primary diagnosis of presumed cause for dementia while allowing for additional diseases that may contribute to the dementia syndrome or may simply be present without clinical consequence [87]. Unfortunately, clinical diagnostic precision is often relatively poor [71] leading to the use of neuropathological findings as the presumed "gold standard" of disease etiology.

While neuropathological brain examination should remain the gold standard basis for clinical–pathological correlation, neuropathological findings, by definition, reflect the sum of all injury during life, including time preceding and after the onset of clinical dementia. Therefore, comorbid pathologies may be deemed less or more relevant than timely in vivo measures might indicate (e.g., the occurrence of stroke years after the onset of what would otherwise be a dementia typical of AD versus the presence of asymptomatic cerebral infarction seen on brain imaging prior to the onset of otherwise typical AD dementia). A specific or even primary pathological diagnosis, when in vivo evidence is not available, could lead to misconceived etiologies of dementia even after post-mortem examination.

Understanding of the complexities of multi-factorial dementias is further complicated by the lack of distinct clinical manifestations of the various brain diseases when seen in combination. For example, vascular disease is traditionally felt to cause disproportional impairments in executive function while relatively sparing memory performance. A comprehensive study of individuals with various degrees of cerebrovascular disease showed that the influence of cerebrovascular disease was generally clinically under-estimated, particularly in the presence of AD pathology [105]. A follow-up study on a similar group of subjects confirmed that AD pathology tends to have a disproportional effect on cognitive ability when viewed at autopsy [23]. Similar difficulties occur in understanding the pathology of other mixed diagnoses, such as Lewy body dementia [93] or the Lewy body variant of AD [44].

The challenges of assessing the impact of mixed pathological processes are also complicated by the fact that certain pathologies, such as cerebrovascular disease, are extremely common and can have a variable period of exposure that could contribute to brain injury. Hypertension and diabetes are two common examples. The prevalence of hypertension increases with age reaching nearly 100 percent prevalence above age 80 [127, 143]. Diabetes has a similar age-related increase in prevalence, although it does not reach the same population exposure as hypertension [85]. Both medical illnesses (specifically mid-life hypertension) are known risk factors for dementia [139],

but individual exposures may vary from years to decades making causal deductions for dementia etiology more difficult, particularly because they may influence cognition independent of "obvious structural MRI changes" [149]. For example, cerebral atrophy, which is a common consequence of vascular risk factors and occurs early in life in the absence of obvious cerebrovascular brain injury and is associated with cognitive impairment [37, 79, 135], is not generally well quantified pathologically. A similar lack of defined pathology exists for white matter injury despite the evident risk for clinically relevant cognitive impairment [29]. Finally, the potential influence of common medical illnesses as they relate to the concept of "mixed pathology" is made more difficult by the absence of a "healthy brain" when it comes to pathological diagnosis [27, 62]. This limitation may complicate interpretation of the pathological correlates of various common medical illnesses as well as advanced aging [24].

In summary, while neuropathological assessments remain important to determine disease etiology and clinical neuropathological associations, in vivo measures are necessary to understand time course relationships.

Clinical evidence for the influence of mixed pathologies on cognition

In this section, we first discuss available biomarkers of specific disease processes separately followed by a summary of available data related to mixed pathologies. A comprehensive review of the literature related to biomarkers of dementing disorders which includes considerable work on cognitive, CSF and imaging measures is beyond the scope of this review, however, a brief summary creates the foundation for clinical studies that examine the interaction of AD, particularly with the two most common disease pathologies: cerebrovascular and Lewy body disease.

Biomarkers of specific dementing diseases

AD

The hallmark clinical features of AD include episodic memory impairment [1] followed by either executive dysfunction or semantic memory impairment [15], although this sequence of clinical features can be variable and specific subtypes of AD dementia exist such as primary progressive aphasia [41], posterior cortical atrophy [123], and frontal variants [144], rendering episodic memory loss as the hallmark of AD less reliable, particularly early in the course of the illness. Lack of a concise and sensitive cognitive biomarker of AD has led to the widespread use of

ancillary testing, particularly CSF and imaging markers, which have been codified into a number of recent diagnostic guidelines [34, 52]. The advent of amyloid [69] and more recently tau [145] imaging in combination with well-established MRI analyses [32, 117] have revolutionized the concept of AD pathophysiology in the clinical setting [53, 121]. With these technologies, AD is no longer considered only a pathological diagnosis, but a chronic disease diagnosed clinically whereby onset, natural history risk and protective factors as well as various treatments can be studied in vivo. Such advances also offer the opportunity to examine the interaction of AD with other measurable pathologies during life.

Cerebrovascular disease

Contrary to AD pathology, which has only recently become visible during life, cerebrovascular disease has a long and established history of early detection and treatment. In fact, most reliable clinical criteria for vascular dementia (VaD) include a combination of cognitive impairment temporally associated with clinical stroke in association with imaging evidence of cerebral infarction [107]. The advent of advanced imaging techniques such as MRI, however, has led to identification of various, asymptomatic processes [78, 134], the clinical significance of which are widely debated [106]. Unlike AD, it is the clinical phenotype of VaD that remains most elusive. Despite multiple efforts to define a specific phenotype [31], a more general consensus has emerged around the concept of vascular contributions to cognitive impairment [99, 118], particularly as it relates to "small vessel disease" [134]. In one of the largest studies to compare cognition and MRI between AD and VaD, Logue et al. [77] found that measures of global atrophy were essentially identical between the two diseases and that as many as 25% of VaD subjects had extreme hippocampal atrophy. Moreover, the extent of white matter hyperintensity (WMH) burden predicted both cerebral and hippocampal atrophy for both dementia groups. Hippocampal atrophy also was significantly associated with mini-mental status examination (MMSE) scores for both groups. Conversely, WMH was independently associated with MMSE scores in VaD, but not AD subjects. These findings led the authors to conclude that "These results strongly suggest a consistent relationship between clinically recognized dementia and tissue loss independent of etiology..." Unfortunately, this study, like many other clinical studies, was limited by lack of awareness of the contribution of concomitant AD pathology, which is estimated to be about 50% in population-based neuropathological studies of clinically defined VaD subjects [70] making clear conclusions about the clinical phenotype of "pure" VaD difficult. As discussed

below, however, the advent of in vivo biomarkers of AD pathology enables detailed examination of the interaction between vascular brain injury and AD pathology on cognitive impairment.

Lewy body disease

The clinical definition of dementia with Lewy bodies (DLB) has consistently focused on the motor aspects of Parkinsonism in the setting of dementia [82]. Current clinical guidelines also include additional features of fluctuating cognition, well-formed visual hallucinations [83] and REM sleep disorder [14]. In addition, patients suffering with DLB are thought to have differing neuropsychological profiles. While AD is characterized by more prominent declarative memory impairment, the cognitive impairments of DLB emphasize more pronounced visuoperceptual, attentional, and verbal fluency impairments [63]. Despite confirmation of these differences in patients followed to autopsy and accounting for the extent of concurrent AD pathology [102], the clinical diagnostic accuracy remains relatively low [93]. This was felt to be due to the insensitivity of clinical specificity of the presence of Lewy bodies among individuals with moderate dementia and increased attribution of Lewy bodies to motor slowing in advanced dementia.

Neuroimaging of DLB shows similarly low sensitivity even using more advanced PET ligands such as amyloid and tau [39]. Alternative measures such as dopamine transporter imaging, however, may be more promising [38], but have yet to be tested in large prospective studies. DLB like VaD, therefore, is a pathological process occurring commonly in the setting of concurrent AD pathology. Unlike vascular disease, however, accurate in vivo markers are not as well developed, leaving the clinical assessment of Lewy body pathology in mixed dementias less certain.

Summary of biomarkers

Recognition that mixed brain pathologies are common to cognitive impairment and dementia, particularly in community-based studies [8] and the oldest old [64] has led to revised concepts of dementia etiology [86] and the potential role of treatment strategies [10]. For this new approach to be effective, however, precise and accurate biomarkers of disease pathologies must be available. CSF along with neuroimaging studies appears promising with regard to identification of AD and CVD pathologies, but further work is clearly needed with regard to alpha-synuclein. In the next section, we summarize available in vivo data that support evidence of independent and additive

effects of the most common mixed form of dementia: AD plus CVD.

While biomarkers for these "big three" will certainly help to clinically evaluate the vast majority of mixed pathologies in dementia, more work is still needed and newer data suggest that other, yet, clinically undetectable processes such as hippocampal sclerosis and TDP-43 relocation contribute significantly to cognitive decline among older individuals even with other pathologies are taken into account [91].

Evidence for the independent, but combined effects of AD and CVD pathologies on dementia

In 1992, the State of California AD diagnostic and treatment centers, led by Dr. Helena Chui, proposed criteria for the diagnosis of ischemic vascular dementia [22]. Unique to this guideline was the notion that "These criteria [should] broaden the conceptualization of vascular dementia, include the results of neuroimaging studies, emphasize the importance of neuropathologic confirmation, refine nosology, and identify areas that require further research. Parallel use of the proposed definitions of "possible" and "mixed" categories in the diagnosis of both AD and IVD would ensure compatibility between ... criteria for AD and the ... criteria for IVD". Taking this conceptual approach, Dr. Chui proposed the ischemic vascular dementia (IVD) program project (PO1-AG12435), designed to elucidate how CVD causes cognitive impairment, either alone or in combination with AD. This prospective, longitudinal study included initial identification of individuals with memory impairment and modest cerebrovascular brain injury as seen on MRI. Early cross-sectional imaging studies showed that regional atrophy measures were most strongly associated with cognition in this cohort [36], although follow-up pathological studies also suggested that in more than 50% of the individuals, hippocampal atrophy may have a vascular origin [130]. Longitudinal analysis of the same cohort revealed a more complex relationship between regional atrophy, particularly hippocampal atrophy, and cognition [88]. In this analysis, individuals without evidence of subcortical lacunes showed a highly significant relationship between hippocampal volume and cognition. For individuals with lacunes, however, this relationship was significantly weaker suggesting that more widespread injury to cortical systems was coincident. In a follow-up study, Mungas et al. [89] further examined the relationship between longitudinal differences in MRI measures and cognitive change. This approach enabled modeling of the impact of incidence lacunar infarcts on cognitive trajectories which showed subtle, but clear evidence of decline in cognitive

ability associated with incident lacunar infarcts. Follow-up neuropathological studies that examined the role of vascular brain injury on cognition [23] and MRI measures [54] showed that AD pathology often overwhelmed mild cerebrovascular disease with respect to cognitive ability, but that the two processes often combined to affect MRI measures, particularly global atrophy.

Given evidence that AD pathology has an overwhelming effect on cognition in the setting of mild vascular disease, the approach of the program project was revised to include individuals with more substantial and symptomatic vascular disease. In addition, amyloid imaging was introduced. Results of cross-sectional studies by Marchant et al. [80] found that vascular brain injury—defined by the presence of extensive WMH and infarction on MRI—have an early and independent effect on cognition, even amongst those who have associated amyloidosis. Follow-up studies found that vascular disease results in increased cerebral atrophy even in cortical areas considered to be primarily affected by AD pathology [128] and that regional atrophy mediates memory loss [129].

The independent effects of amyloid and vascular brain injury have been further examined in a series of eloquent studies on subcortical vascular dementia (SIVD) [66, 67, 77, 101, 146]. This unique group of patients was defined as meeting DSM-IV criteria for vascular dementia in the presence of severe WMH, without accompanying lacunar infarctions, but without evidence of territorial infarction or macrohemorrhage on MRI [77]. Initial studies found that nearly 70% of the patients had no significant amyloid accumulation on PET scan. There were no differences in clinical symptomatology, vascular risk factors or hippocampal atrophy between those with and without extensive amyloidosis. Immediate and delayed recall, however, was significantly worse among SIVD subjects with extensive amyloidosis suggesting a subtle but independent effect of amyloid on memory performance in the presence of SIVD. In addition, CVD and AD measures were found to be uncorrelated supporting the notion of independent effects [101]. Further analyses of this amyloid negative SIVD cohort found significant cortical thinning, but in a pattern somewhat different from AD [66]. These differences in cerebral atrophy also appear to differentially affect baseline [146] and longitudinal [67] cognitive function, although the ability to clinically differentiate VaD from AD on an individual basis remains difficult [147].

While these studies examined the independent but additive impact of CVD and AD pathologies, other studies suggest that intraparenchymal amyloidosis on PET imaging may also be increased in relationship to vascular risk factors [48] suggesting the possibility for both interactions as well as independent processes. Because older cohorts may not have granular details on blood pressure, vascular risk factors, pathology, and cognition, further studies of younger individuals with vascular risk factors may help to clarify this issue.

Summary and future directions

In summary, the advent of molecular imaging combined with MRI has enabled specific studies of the in vivo effects of the often-combined CVD and AD pathologies. Preliminary evidence supports the notion of independence of these two processes on the types of brain injury as well as the influence on cognitive processes, confirming pathological data previously available. This evidence makes it likely that the co-occurrence of CVD increases dementia risk in later life as suggested by risk factor analyses based on epidemiological studies [68], and points to potential therapeutic interventions that may substantially reduce dementia incidence through the aggressive control of vascular risk factors [10, 30]. At the same time, because pathologies are often mixed, it is important to address common underlying risk factors and biologic mechanisms of degeneration in future research. For instance, common genetic risk variants may increase risk of multiple forms of pathology (e.g., apoE e4 is related to risk of amyloid deposition, CAA, LB and to a lesser degree cerebral infarcts [47]); and inflammatory mechanisms may be a mechanism of injury in multiple neurodegenerative and vascular diseases. Finally, though there have been strong advances in biomarkers there is a strong need for further in vivo work with biomarkers of other specific pathologies including small vessel vascular disease, LB, TDP-43, and HS to successfully study the prevention, diagnosis and treatments of mixed dementia.

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