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Featured Articles

Magnetic resonance imaging-measured atrophy and its relationship to cognitive functioning in vascular dementia and Alzheimer's disease patients

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Abstract

Background: Recent pathological studies report vascular pathology in clinically diagnosed Alzheimer's disease (AD) and AD pathology in clinically diagnosed vascular dementia (VaD). We compared magnetic resonance imaging (MRI) measures of vascular brain injury (white matter hyperintensities [WMH] and infarcts) with neurodegenerative measures (medial-temporal atrophy [MTA] and cerebral atrophy [CA]) in clinically diagnosed subjects with either AD or VaD. We then examined relationships among these measures within and between the two groups and their relationship to mental status.

Methods: Semi-quantitative MRI measures were derived from blind ratings of MRI scans obtained from participants in a research clinical trial of VaD (N = 694) and a genetic epidemiological study of AD (N = 655).

Results: CA was similar in the two groups, but differences in the mean of MTA and WMH were pronounced. Infarcts were significantly associated with CA in VaD but not in AD; MTA and WMH were associated with CA in both. WMH was associated with MTA in both groups; however, MRI infarcts were associated with MTA in VaD but not with MTA in AD patients. MTA was strongly associated with Mini-Mental State Examination scores in both groups, whereas evidence of a modest association between WMH and Mini-Mental State Examination scores was seen in VaD patients.

Conclusions: MRI data from two dementia cohorts with differing dementia etiologies find that the clinical consequences of dementia are most strongly associated with cerebral and medial-temporal atrophy, suggesting that tissue loss is the major substrate of the dementia syndrome.

Keywords: Alzheimer's disease; MRI; Dementia; Vascular; Hippocampus; Atrophy

1. Introduction

Research on dementia has focused on understanding and differentiating dementia subtypes to identify clinical and pathophysiological characteristics unique to each disorder. However, data strongly suggest that late-life dementia,

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commonly attributed to Alzheimer's disease (AD), is actually a complex process often because of the combined effects of multiple pathologies [1]. Magnetic resonance imaging (MRI) is one method by which the extent, impact, and possible etiology of regional brain pathology can be quantitatively assessed [2]. Early attempts to compare MRI measures among clinically diagnosed AD and vascular dementia (VaD) subjects, however, were relatively small and inconclusive [3]. More recent reports of the qualitative assessment of MRI differences between AD and VaD patients with larger samples have suggested that medial-temporal atrophy (MTA), particularly hippocampal atrophy, is uniquely associated with clinical AD as opposed to VaD [4]. In fact, hippocampal atrophy is considered the imaging hallmark of clinical AD and is strongly associated with AD pathology [5–8]. Bastos-Leite et al, however, reported a high rate of MTA in a well-characterized sample of VaD patients and an association of MTA with cognitive functioning in the same group [9]; similarly other MRI studies have found extensive hippocampal atrophy in patients with suspected VaD [10] and hippocampal sclerosis has been associated with severe hippocampal atrophy on MRI [2]. Global cerebral atrophy also has been associated with cognitive performance in both AD and VaD patients [11]. Although VaD has characteristically been associated with white matter hyperintensities (WMH) in addition to infarction, WMH have been negatively correlated with cognitive functioning in persons with normal cognition, VaD [12], mild cognitive impairment [2], and AD [13], suggesting that the effect of this pathology transcends clinical diagnosis.

Given the evidence for the complex nature of brain diseases underlying the dementia syndrome, we therefore sought to investigate the relative effect of cerebral atrophy, MTA, WMH, infarcts, and Mini-Mental State Examination (MMSE) scores among cognitively normal, AD, and VaD individuals. To accomplish this aim, we first characterized the different levels of atrophy and vascular pathology observed in each group. We then examined the functional relationships between atrophy, vascular pathology, and cognitive impairment within the AD and VaD groups. Given the presumption that VaD is solely because of vascular pathology, we hypothesized that MRI infarcts and WMH should be strongly associated with global cerebral atrophy (CA) in the VaD group. Conversely, given that the dementia attributable to AD is solely because of AD pathology, we hypothesized that MTA—as an excellent marker of AD pathology—would be strongly associated with CA in the AD group. To test the possibility, however, that hippocampal atrophy can result from either vascular or AD pathology [2], we also examined the relationship between MTA and vascular markers. We again hypothesized that MTA would be weakly associated with vascular markers (white matter hyperintensity and stroke) in the VaD group and unassociated with vascular markers among the AD subjects. Finally, we investigated the relationship between all the MRI and cognitive ability (MMSE) within the two dementia groups. We hypothesized that vascular markers would have a stronger association with MMSE in the VaD group, but that MTA would have the strongest association with MMSE in the AD group.

2. Methods

2.1. Subjects

We studied VaD patients diagnosed using Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, AD patients diagnosed using National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and cognitively normal relatives (mostly siblings) of the AD patients. A total of 826 randomized subjects meeting NINDS-AIREN criteria for VaD were recruited for an industry-sponsored clinical trial evaluating the safety and efficacy of donepezil in VaD, of which approximately 31% met clinical criteria for probable VaD [14] (clinicaltrials.gov NCT00165737); 655 AD patients meeting NINCDS-ADRDA criteria for AD and 756 cognitively normal (CN) relatives of the AD patients were Caucasian participants of the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study, a multisite, multiethnic, family-based genetic study of AD [15–17]. The recruitment and evaluation of MIRAGE subjects was overseen and approved by Boston University Human Subjects Protection Committee. Ethics review panels appropriate for clinical trials also oversaw VaD subject collection and study design. Written consent was obtained from all subjects (or guardians of subjects).

2.2. Data

Both the MIRAGE and VaD studies were large multicenter studies. MRI scanner strength, model, and settings used varied by collection site, necessitating the use of semi-quantitative measures of atrophy and vascular disease. All MRI scans were scored by a single rater (C.D.) blinded to screen failure status in the VaD study and AD status in the MIRAGE study (proband vs control). Although the rater was aware of the study for which the person was recruited, he was blinded to clinical syndrome in both studies as MIRAGE included both AD and normal controls and the VaD study included both VaD and AD patients. Among the 826 VaD subjects, 132 did not receive an MRI and were excluded from comparisons other than basic descriptive statistics. Scans were scored for left and right MTA using Scheltens' scale (0-4 integer, where most severe atrophy = 4), cerebral infarction (presence/absence), and number of infarcts (NI). The average MTA (left and right) was used as our measure MTA in analyses described later. Global atrophy and WMH were rated on a visual analog scale (0-100), with 100 representing severe atrophy and extreme WMH,

Table 1
Demographic characteristics

Characteristic	CN N = 756	AD N = 655	VaD N = 826
Demographics			
Age (years)	69.43 (SD = 9.04)	74.17 (SD = 8.73)	73.52 (SD = 9.14)
Sex			
Male	287 (38%)	255 (39%)	329 (40%)
Female	469 (62%)	400 (61%)	497 (60%)
Years of education			
≤8	98 (13%)	121 (19%)	22 (12%)
9–12	278 (37%)	273 (42%)	79 (41%)
>12	374 (50%)	258 (39%)	78 (41%)
Medical history			
Stroke	32 (4%)	56 (9%)	706 (85%)
Hypertension	377 (51%)	306 (47%)	656 (79%)
Smoking	332 (44%)	256 (39%)	500 (60%)
Diabetes	70 (9%)	83 (13%)	143 (17%)
Hyperlipidemia	338 (46%)	271 (43%)	411 (50%)
TIA	17 (2%)	27 (4%)	114 (14%)
Psychometric scores			
MMSE	NA	18.17 (0.35)	22.65 (0.18)
MRI measures	CN	AD	VaD
	N = 756	N = 655	N = 694
Mean atrophy (0-100)	49.23 (SD = 11.64)	62.40 (SD = 11.84)	64.13 (SD = 14.13)
Mean WMH (0-100)	8.97 (SD = 15.26)	19.06 (SD = 22.18)	30.32 (SD = 26.37)
Mean MTA (0-4)	0.80 (SD = 0.92)	2.48 (SD = 1.16)	1.88 (SD = 1.05)
Cerebral infarction	105 (14%)	150 (23%)	451 (66%)

NOTE. Numbers in parentheses represent standard deviation or proportion for frequency data.

respectively, as previously reported [18]. The method used tie points that were derived from quantitative analysis of brain and WMH as shown in the Supplemental Figs. S1–S3. This approach has been proved to have clinical diagnostic significance for differentiating cognitively normal individuals from those suffering from AD [18] and conversion of mild cognitive impairment to dementia [19]. MRI infarcts were identified based on imaging characteristics [20] and further defined as small (maximum diameter: <1 cm) or large (maximum diameter: ≥1 cm). Finally, the total NI was recorded and ranged from 0 to 10. Cognitive functioning in both patient samples was measured using the MMSE [13].

2.3. Analysis methods

Data analysis was performed with *R* [21]. Means were compared with an analysis of variance, and Tukey's HSD test (corrected for unequal sample sizes) was used to evaluate pair-wise comparisons. The relationship between vascular markers atrophy and cognitive functioning was evaluated in a series of regression models. The regression models and parameters examined were specified in advance, guided by the hypotheses stated in the Introduction section. All models examined are presented. Regression predictors were evaluated by examining the estimated β weights with all predictors in the model. Separate regression models were estimated for AD and VaD. To evaluate their relative importance, continuous predictors and responses were standardized (mean = 0, variance = 1) and β estimates can be interpreted as correlations. R^2 estimates were compared using a normal approximation appropriate for large samples [22]. Age and gender were included as covariates in all regression models to minimize possible confounding. Gender is coded as females = 0 and males = 1, so that positive β estimates for the gender effect indicate higher scores for males and negative β estimates indicate higher scores for females. To compare models between AD and VaD groups, an additional pooled analysis was performed which estimated an interaction term representing the difference in β estimates for the two groups. The significance of this term indicates the degree to which the associated predictor has a different effect in AD and VaD subjects.

3. Results

Demographic information is presented in Table 1. The subjects in the CN group were younger as compared with either of the dementia groups ($P < .0001$). Vascular risk factors were lower in the CN and AD groups as compared with the VaD subjects ($P < .03$). Box plots of MTA, global atrophy, WMH, and NI are shown in Fig. 1. For all MRI ratings, the CN group had the lowest score, with the VaD group showing the highest scores on global atrophy ($F_{df = 2,2071} = 303.14$; $P < .0001$), white matter hyperintensities ($F_{df = 2,2079} = 175.82$; $P < .0001$), and number of infarcts ($F_{df = 2,2050} = 282.25$; $P < .0001$). The AD group showed the highest MTA scores ($F_{df = 2,2014} =$

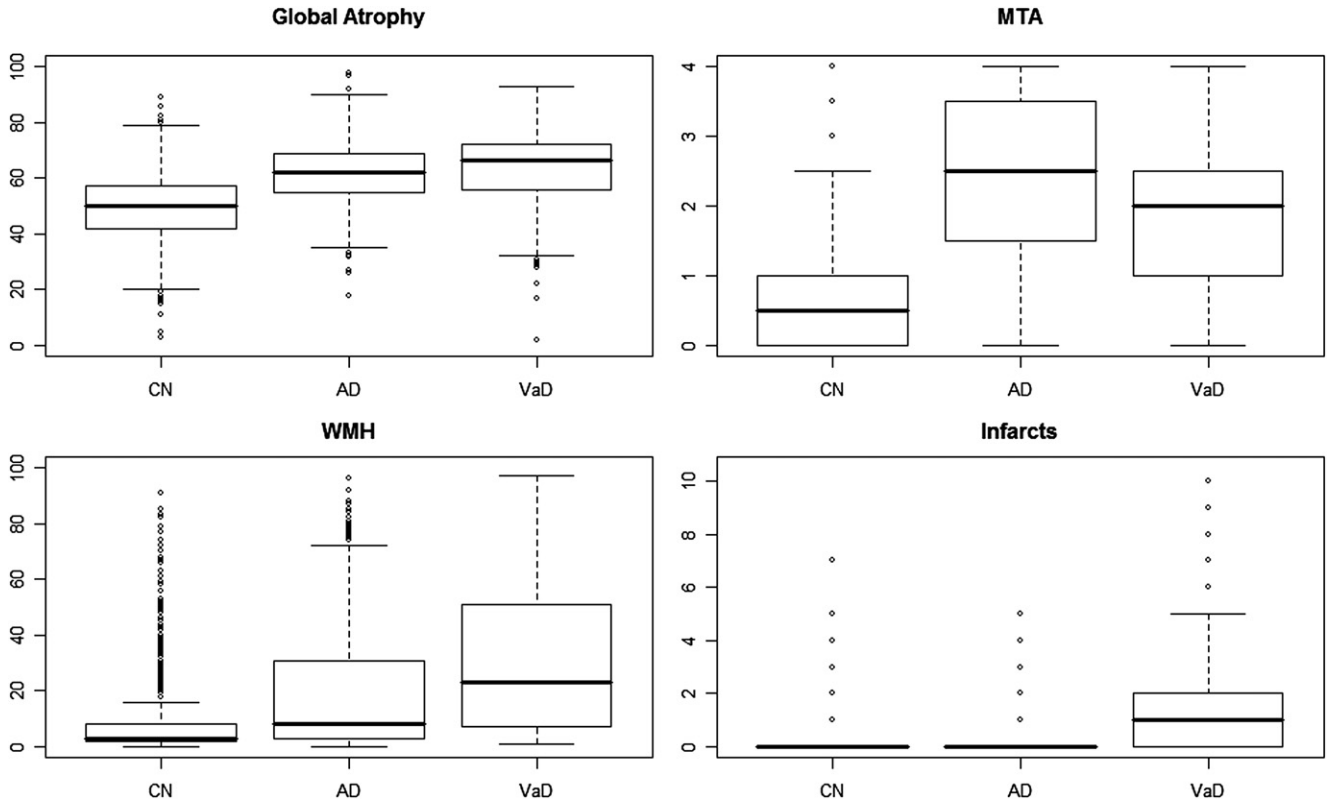

Fig. 1. Box plots of global cerebral atrophy ratings, medial temporal atrophy, white matter hyperintensity, and number of infarcts. Key: CN, cognitively normal; AD, Alzheimer's disease cases; VaD, vascular dementia cases. Bold lines represent median, boxes show inter-quartile ranges. Whiskers extend to data within 1.5 times the inter-quartile range from the box. Outliers (points >1.5 times the inter-quartile range) are presented as circles.

466.04; $P < .0001$). Differences between the VaD and AD group were significant for global atrophy ($P < .035$), WMH ($P < .0001$), and MTA ($P < .0001$). The prevalence of infarcts for AD subjects, although higher, was not significantly different from that of CN ($P = .0641$). The distribution of MTA scores separated by left and right hemisphere is displayed in Fig. 2. Although AD subjects generally had high MTA ratings and CN had low ratings, the VaD group showed a substantial proportion of subjects at each MTA rating except 0.

As expected, VaD had a substantially higher prevalence of large infarcts (39%) as compared with AD (5%) and CN (2%). Significant differences in the prevalence of both large and small infarcts between VaD and AD subjects were also noted, although 34% of VaD subjects did not have a detectable infarct on MRI.

For the next stage of the analysis, regression models were analyzed to compare the pathological processes underlying these two samples. First, we examined the relationship between WMH, NI, and MTA on global atrophy. Among VaD patients, age, gender, NI, WMH, and MTA were significantly related to CA ($F_{df = 5,608} = 67.34$; $P < .0001$) and all predictors contributed to the model (all $P < .025$). The model was also significant in the AD group ($F_{df = 5,612} = 44.45$; $P < .0001$) but only age, WMH, and MTA contributed to the model ($P < .02$). The model accounted for CA in VaD patients ($R^2 = 0.356$) significantly more precisely ($P = .025$) than for AD patients ($R^2 = 0.266$) (Table 2). The model estimates for the VaD group remained nearly identical after eliminating approximately one-third of the VaD group without infarcts—those subjects most likely considered to be suffering from the combined effects of AD and vascular pathologies.

Next, we explored the relationship between MTA and vascular markers (WMH and stroke [yes/no]) (Table 2). Among VaD patients, both presence of stroke and WMH contributed significantly to MTA ($P < .04$; $R^2 = 0.163$), but in opposite directions, with increasing WMH associated with worsening MTA scores, but the presence of stroke associated with improved MTA scores. Conversely, among AD patients, only age and WMH contributed significantly to the model predicting MTA, with increasing WMH associated with worsening MTA scores ($P < .0001$; $R^2 = 0.173$). A summary of this model (model 2) including coefficient estimates and their significance is given in Table 2.

Finally, we investigated the relationship between MRI measures and cognitive ability (MMSE) to test our hypothesis that the various MRI measures would show different associations with cognition because of the different etiologies of dementia. Surprisingly, MMSE scores were associated with MTA in both VaD ($F_{df = 3,619} = 31.19$; $P < .0001$; $R^2 = 0.131$) and AD ($F_{df = 3,317} = 14.79$; $P < .0001$; $R^2 = 0.123$). Details of this model (model 3) are shown in Table

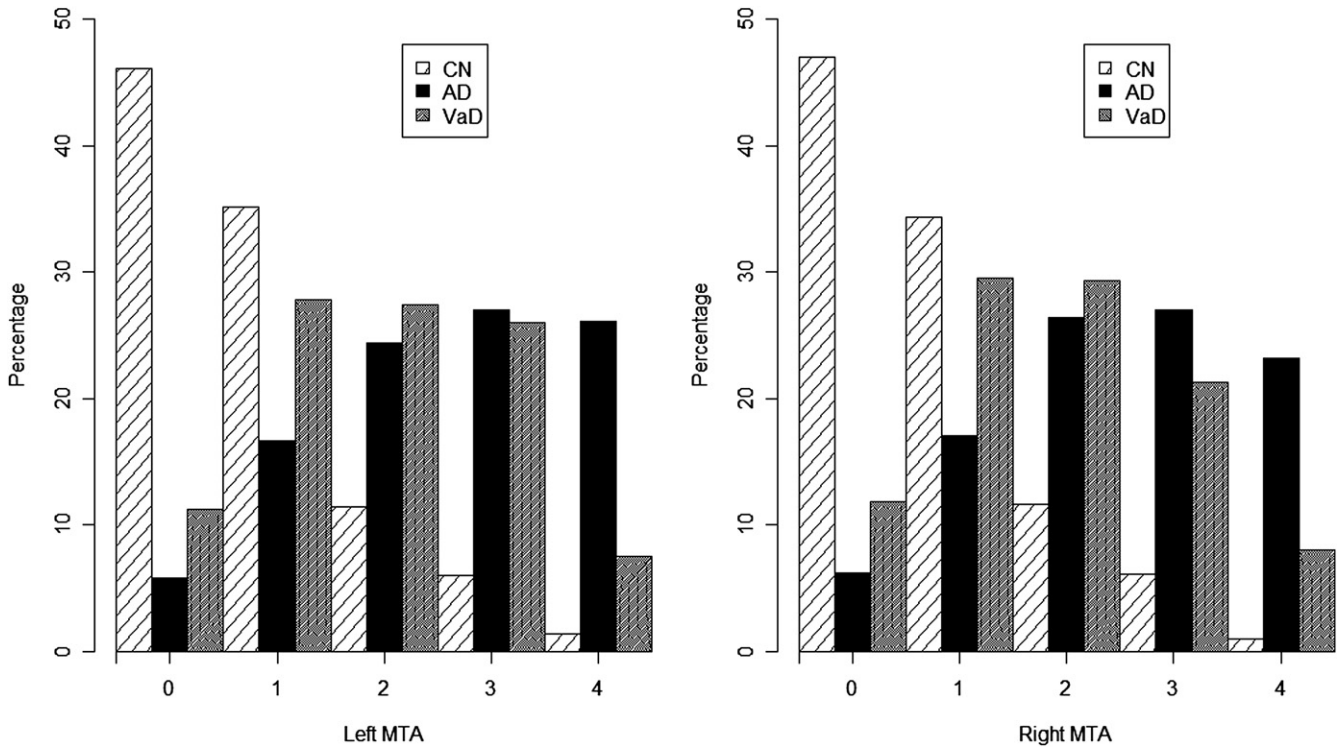

Fig. 2. Left and right MTA distribution for cognitively normal (CN), Alzheimer disease cases (AD), and vascular dementia cases (VaD). Key: Scheltens' scale: 0-4 integer scale with most severe atrophy = 4.

2. Examining vascular factors in relation to MMSE scores, we found significant associations between MMSE and WMH in the VaD group ($P < .005$), but this association explained only a limited amount of additional variance ($R^2 = 0.039$) in MMSE. There was no association between WMH and MMSE for the AD group ($P = .2654$; $R^2 = 0.017$). The covariate estimates and significance levels are summarized in Table 2: model 4.

4. Discussion

We examined brain MRI measures in large samples of VaD, AD, and cognitively normal controls. Expected large differences in MTA, WMH, and NI were found between VaD and AD subjects. Although the mean global cerebral atrophy differed between the VaD and AD subjects, the magnitude of this difference was rather small—a difference of less than 2 on a (0-100) scale. From these findings, we conclude that loss of brain tissue accompanies clinical dementia, regardless of etiology. We also note that age was significantly associated with brain atrophy in both groups but more strongly among VaD than AD patients, despite very similar age distributions. This finding suggests that normal aging and vascular disease interact in the VaD group, whereas AD pathology appears to overwhelm age-related differences. In addition, we note not only the expected finding of a significant association between infarcts and CA within the VaD group, but also a significant inverse relationship between infarcts and CA within the AD group. We hypothesize that the inverse association between infarcts detected on MRI and CA within the AD group indicates an additive effect of infarcts for dementia in AD such that less AD pathology is necessary to develop dementia among those with concomitant vascular pathology [1,23,24]. Other studies [25] have emphasized, in unselected samples, the importance of vascular pathology in cognitive functioning within AD samples. The lack of association with infarcts and MMSE in our AD sample may largely reflect the sampling methods used as our AD sample was selected for minimal vascular pathology.

Consistent with recent findings, MTA was strongly associated with CA in both dementia groups, even after excluding VaD patients with no infarcts to reduce the likely contamination of this group by mixed pathologies. As a consequence, we suspect that AD pathology was much less common within this latter group [26], and yet, we note that the relationship between MTA and CA did not change. The cause for this association is unclear, but hippocampal sclerosis (HS) does occur in vascular cognitive impairment [2] and is associated with profound hippocampal atrophy. It is, therefore, possible that some of the association between CA and MTA in the VaD group represented shared vascular injury to the cerebrum and hippocampus, respectively.

We observed a complex relationship between vascular disease and MTA. Stroke was not associated with MTA

Table 2
Regression models

	Cohort	VaD		AD		Comparison
Response	Predictor	β estimate	Pr(>|t|)	β estimate	Pr(>|t|)	Pr(>|t|)
Model 1: Predictors of CA in the VaD and AD cohorts						
CA	Sex	−0.16	0.020	0.14	0.052	0.0027
	Age	0.23*	$<10^{-5}$	0.094*	0.016	0.014
	Infarcts (count)	0.094*	0.0059	−0.065*	0.076	0.0015
	WMH (1-100)	0.18*	$<10^{-5}$	0.15*	1.6×10^{-4}	0.61
	MTA	0.38*	$<10^{-5}$	0.41*	$<10^{-5}$	0.66
Model 2: Predictors of MTA in the VaD and AD samples						
MTA	Sex	−0.19	0.016	−0.015	0.84	0.11
	Age	0.28*	$<10^{-5}$	0.33*	$<10^{-5}$	0.41
	WMH (1-100)	0.21*	$<10^{-5}$	0.16*	$<10^{-5}$	0.35
	Stroke (Yes/No)	−0.23	0.033	0.095	0.48	0.06
Model 3: Impact of MTA on cognitive ability (MMSE score)						
MMSE	Sex	−0.0064	0.93	0.10	0.33	0.40
	Age	−0.035*	0.37	0.067*	0.25	0.14
	MTA	−0.34*	$<10^{-5}$	−0.38*	$<10^{-5}$	0.56
Model 4: Impact of vascular disease markers on cognitive ability (MMSE score)						
MMSE	Sex	0.018	0.82	0.083	0.46	0.63
	Age	−0.12*	0.0021	−0.094*	0.12	0.71
	WMH (1-100)	−0.13*	6.1×10^{-4}	−0.049*	0.42	0.25
	Stroke (Yes/No)	−0.081	0.44	0.019	0.92	0.65

*β estimate can be interpreted as a correlation coefficient.

among AD subjects but was associated with *less* MTA among VaD subjects. Furthermore, WMH was significantly associated with worse MTA scores in both groups. These seemingly disparate results may be reconciled through consideration of the potential mechanisms leading to WMH and macroscopic infarcts. In a study of subcortical vascular cognitive impairment [27], Chui et al observed greater WMH and HS in the subcortical vascular disease group as compared with the AD group. Subsequently, these investigators reported significant univariate associations of WMH with HS [2], suggesting that vascular medial-temporal injury may result from small, rather than large vessel cerebrovascular disease. The association between WMH and MTA in the VaD group found here, therefore, might reflect a similar relationship with large vessel cerebrovascular disease causing more cortical infarcts and dementia, while preserving hippocampal integrity, but small vessel cerebrovascular disease causing increased WMH and hippocampal injury. It is also intriguing to suggest that small vessel cerebrovascular disease association with WMH in AD may also contribute to hippocampal injury [28]. However, it is also possible that WMH in AD might result from an alternative neurodegenerative pathway [29], leading to a significant association between MTA and WMH for alternative reasons. These intriguing hypotheses require further research.

Despite pathological differences between AD and VaD, we found MTA and MMSE scores were correlated in both groups. MTA values were strongly and equally associated with cognition in both groups, explaining approximately 13% of the variance in MMSE scores, whereas vascular measures, particularly WMH, were associated with cognition only in the VaD group, but explained only a small amount of variance (4%). These findings suggest that neuronal cell loss (as exemplified by atrophy) is specific to cognition, independent of dementia etiology.

Use of a single rater for MRI-based scales of atrophy and cerebrovascular health presented a unique opportunity despite several limitations. First, the rater was not blind to the study of origin; however, again we stress that the studies contained AD subjects and either VaD subjects or controls, and the rater was blind to diagnosis within study. Second, the observed relationships among vascular measures, atrophy, and cognitive functioning in these uniquely ascertained cohorts where the diagnostic criteria are designed to minimize the inclusion in either group of subjects with pathophysiology more characteristic of the other group cannot be generalized to clinical populations. Thus, it would be inappropriate to develop diagnostic recommendations based on parameter estimates obtained here. Third, our use of semi-quantitative measures may reduce sensitivity to group differences. Of course, the large sample size as compared with previous studies would mitigate any lack of power caused by using semi-quantitative measures. Moreover, the use of semi-quantitative measurements may also be a strength, as this would tend to reduce artificial differences between groups which may arise because of subtle differences in the MRI machines and specific scan parameters used at each study site. Finally, because these data are

cross-sectional, one cannot assess the rate of atrophy in an individual or use these data to predict the transition from a nondemented to a demented state.

VaD is radiologically defined by large- and small-vessel infarction that can include multiple basal ganglia and white matter lacunes, bilateral thalamic infarctions, or large hemispheric infarctions with or without accompanying extensive WMH [30]. Large cortical infarctions, multiple lacunae, and thalamic infarcts are each sufficient to cause vascular dementia in the setting of limited AD pathology [26,31], whereas the potential role of extensive WMH in dementia is less clear [27,32]. Like previous reports [30], these analyses identified a significantly increased prevalence of vascular risk factors and MRI evidence of vascular brain injury in VaD subjects. Similar degrees of generalized brain atrophy were also found for the dementia groups. Unlike the study by Scheltens and Kittner [30], the distribution of MTA measures in these data was significantly different between VaD and AD groups, with less atrophy on an average for the VaD group. Despite differences in MTA distribution, MTA measures remained significant predictors of cognition in VaD patients, confirming a previous report [9]. These results strongly suggest a consistent relationship between clinically recognized dementia and tissue loss independent of etiology, a unique finding of the current study.

These results may impact future clinical trials aimed at primary or secondary prevention of vascular or AD dementias. Although selected treatments may vary, clinical outcomes are likely to be tied to slowing or preventing loss of brain tissue. Furthermore, the role of medial-temporal injury to the dementia syndrome in VaD is an understudied area. Understanding the process by which tissue loss occurs with vascular brain injury—beyond the obvious areas of necrosis from infarction—may provide important new areas for drug development.

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