MRI-leukoaraiosis thresholds and the phenotypic expression of dementia

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ABSTRACT

Objective: To examine the concept of leukoaraiosis thresholds on working memory, visuoconstruction, memory, and language in dementia.

Methods: A consecutive series of 83 individuals with insidious onset/progressive dementia clinically diagnosed with Alzheimer disease (AD) or small vessel vascular dementia (VaD) completed neuropsychological measures assessing working memory, visuoconstruction, episodic memory, and language. A clinical MRI scan was used to quantify leukoaraiosis, total white matter, hippocampus, lacune, and intracranial volume. We performed analyses to detect the lowest level of leukoaraiosis associated with impairment on the neuropsychological measures.

Results: Leukoaraiosis ranged from 0.63% to 23.74% of participants' white matter. Leukoaraiosis explained a significant amount of variance in working memory performance when it involved 3% or more of the white matter with curve estimations showing the relationship to be nonlinear in nature. Greater leukoaraiosis (13%) was implicated for impairment in visuoconstruction. Relationships between leukoaraiosis, episodic memory, and language measures were linear or flat.

Conclusions: Leukoaraiosis involves specific threshold points for working memory and visuoconstructional tests in AD/VaD spectrum dementia. These data underscore the need to better understand the threshold at which leukoaraiosis affects and alters the phenotypic expression in insidious onset dementia syndromes. *Neurology*® 2012;79:734–740

GLOSSARY

AD = Alzheimer disease; **BET** = Brain Extraction Tool; **CDT** = Clock Drawing Test; **DSC** = dice similarity coefficient; **FLAIR** = fluid-attenuated inversion recovery; **ICV** = intracranial volume; **LA** = leukoaraiosis; **P(r)VLT** = Philadelphia (repeatable) Verbal Learning Test; **UMDNJ** = University of Medicine and Dentistry of New Jersey; **VaD** = vascular dementia; **WM** = white matter.

Optimal clinical management of dementia requires an appreciation of MRI-detected leukoaraiosis (LA). LA can alter cognitive dysfunction,[1] everyday living abilities,[2] and anti-cholinesterase effectiveness.[3] It remains uncertain, however, how much LA is needed to alter the dementia phenotypic expression. Some have suggested that 25% of white matter needs to contain LA for dysexecutive impairment to supersede amnestic impairment.[4] This has been shown in 2 separate studies[4,5] using the Junque Scale of LA,[6] a 40-point visual rating scale. When divided into thirds, a Junque score greater than/equal to 18 (suggesting >25% LA) was associated with greater executive vs episodic memory impairment in dementia. A score less than 10 reflected striking anterograde memory impairment. A score between 10 and 17 resulted in similar executive and episodic memory dysfunction.

The present study was designed to further investigate the threshold effect of LA with newer, more objective imaging techniques examining LA as a proportion of white matter while also controlling for intracranial volume which can modify brain structure-function associations.[7,8] It was hypothesized that among dementia patients this method would be positively correlated with the Junque LA Scale, but demonstrate a unique burden threshold only on measures

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heavily dependent on frontal-subcortical networks (executive function and visuoconstruction), but not on measures of language or episodic memory.

METHODS

Standard protocol approvals, registrations, and patient consents. The study was approved by the University of Florida and the University of Medicine and Dentistry of New Jersey (UMDNJ) institutional review boards and followed principles from the Declaration of Helsinki. The study involved retrospective data review from patients involved in the UMDNJ Memory Assessment Program, an outpatient clinic that included evaluations by a neurologist, neuropsychologist, and social worker as well as an MRI study of the brain and laboratory studies conducted within 2 weeks of the neuropsychological evaluation.

Participants. Participants were consecutive patients (n = 83) who met criteria for probable Alzheimer disease (AD)[9] or criteria for the diagnosis of probable/possible ischemic vascular dementia or subcortical vessel vascular dementia (VaD).[10] Clinical diagnosis was not analyzed or used as a grouping variable because of growing evidence of gray matter/vascular pathology overlap[11,12] and the questionable validity of consensus panel diagnostic criteria for VaD.[13] An insidious onset was a feature for all participants with no participant presenting with an ischemic score >4,[14] a sudden onset of cognitive decline or a stepwise course, or focal neurologic signs. Participants were excluded if there was evidence for major depression, large vessel stroke, stepwise decline suggestive of multi-infarct dementia, major medical/CNS disease, seizure disorder, thyroid disease, closed head injury, substance abuse, or other serious psychiatric disorders. Medical records, available for a portion of participants (n = 42), showed risk factors for vascular disease in some patients, i.e., hypertension (present = 31.0%, absent = 40.0%, unknown = 7.1%), hypercholesterolemia (present = 40.5%, absent = 2.4%, unknown = 57.1%), diabetes mellitus (present = 15.7%, absent = 31.0%, unknown = 28.6%). All participants were ambulatory and relatively medically well and stable.

Brain MRI acquisition. Participants completed a clinical brain MRI on 1.5 Tesla GE Signa and Genesis systems. Three-dimensional T1-weighted sequences (repetition time range across scans = 1,238 to 1,467 msec; echo time = 2.5 to 4.6 msec; inversion time = 450 msec; flip angle = 20 degrees; matrix = 320 × 192) were reconfigured to 112 to 120 gapless, 2.4-mm images allowing for image reconstruction into any plane. LA volumetrics were based on 2D fluid-attenuated inversion recovery (FLAIR) protocols (repetition time range across scans = 8,402–12,800, echo time range = 125–147, inversion time range = 1,800–2,200; flip angle = 90 degrees, gap = 5 to 7 mm) with volume calculated using an algorithm for slice thickness and gap. The following imaging variables were obtained by raters blinded to all clinical data and other raters' scores.

Leukoaraiosis. Reliable raters (confirmed via 15 brains blinded and randomized for a total of 45 scans; dice similarity coefficient [DSC] inter-rater range 0.84–0.93; intrarater range >0.99[15]; using in-house macros for ImageJ,[16,17] http://rsbweb.nih.gov/ij/docs/index.html) measured LA which included periventricular caps and rims with semiautomated volumetric measures. LA voxels for each brain slice were thresholded and created into 2D LA binary masks that were then concatenated into a 3D binary mask. This method yielded an estimated total brain LA volume in mm^3. LA also was measured with the Junque LA Scale by a neuroradiologist with excellent intrareliability ($r >$ 0.90). This method yielded a subjective estimate of LA on a scale of 1 to 40.[6]

White matter. The Brain Extraction Tool (BET) from FSL[18] aided extraction of brains from T1-weighted brain MRIs with brain center of gravity and fractional intensity revised by raters to achieve best extraction. BrainSuite9[19] and rater reviews for quality provided prosencephalon masks (minus cerebellum and brainstem). Re-extraction was completed if regions of subcortical gray matter were included in the final white matter mask. The final variable was the estimated total white matter (total WM) volume in mm^3.

Imaging control variables. To control for variations in head size, intracranial volumes (ICVs; brain plus associated CSF with the inner table of the skull as the outer boundary of the segmented image) were created using BET from FSL[18] with manual modifications performed by trained raters. The final variable was the estimated intracranial volume in mm^3. A reliable rater (intrarater $r = 0.98$; via 15 brains blinded and randomized for a total of 45 scans) trained by a neuroradiologist (I.S.) examined each brain for lacunae. Only well-defined, dark lesions with a diameter ≥2 mm that held a stationary position between slices were graded. Lacune volumes were based on the formula of a sphere ($4/3\Pi r^3$), with volumes from each brain summed to obtain an overall volume per subject.[20] Two tracers with excellent inter-rater and intrarater spatial overlap and good volume reliability (inter-rater: grand DSC = 0.80 ± 0.02, intrarater: grand DSC = 0.81 ± 0.05) manually segmented left and right hippocampi using guidelines[21] and ITK-SNAP software.[22] Total (bilateral) hippocampal volume was the final dependent variable.

Neuropsychological assessment. Measures used in prior LA threshold studies[4,5] were repeated in the current study for comparison purposes. All neuropsychological measures were administered and scored by examiners who were blind to the imaging data. Normative data were acquired from associated publications cited below.

Boston Revision of the Wechsler Memory Scale–Mental Control Subtest[23] has been used to examine working memory in dementia, mild cognitive impairment, and healthy control participants.[4,24] The dependent variable was the average accuracy index (AcI = [1 − ([false positive + misses]/no. possible correct)] × 100) for 3 nonautomated tasks (i.e., months backward, alphabet rhyming, and alphabet visualization).

The Clock Drawing Test (CDT[25]) was used to assess visuospatial/constructional and executive functions. In dementia, poor command and copy performance is often seen among individuals with frontal system deficits.[26] Error scores were obtained according to objective criteria[27] and by reliable raters (rater reliability >0.90[28]), with summed command and copy errors serving as the dependent variable.

Philadelphia (repeatable) Verbal Learning Test [P(r)VLT[24,29]] is a 9-word serial list learning test designed for dementia. The dependent variable was the delayed recognition discriminability index score.[29]

Lexical Fluency Index is a measure of language retrieval that combines output on the "animal" fluency task and output for the letter "S" from the "FAS" Controlled Oral Word Association task.[30] A ratio score was calculated (i.e., total "animal" responses/[total animal responses + total "S" responses]); a high score indicates more "animal" vs letter responses, suggesting relatively better lexical access.[31]

Table Participant (n = 83, unless otherwise noted) demographics, bilateral imaging volumes (mm^3), and neuropsychological data

Variable	Mean	SD	Minimum	Maximum
Demographics				
Age, y	80.05	5.35	65.00	91.00
Education, y	12.11	2.96	2.00	20.00
MMSE	22.26	3.39	14.00	29.00
GDS	2.95	2.75	0.00	10.00
LA and white matter, mm^3				
Total WM	325,514.80	41,320.41	201,219.57	431,440.40
Total LA	19,362.10	15,558.75	1,838.59	72,060.74
Proportion LA	0.0611	0.0521	0.0063	0.2364
Junque LA Scale	8.65	5.98	0	30
Imaging control variables, mm^3				
TICV	1,346,270.52	126,561.53	990,262.38	1,613,653.25
Hippocampal	3,709.32	1,005.83	1,464.06	6,643.35
Lacune	17.40	42.10	0.00	231.43
Cognitive scores				
Mental control (n = 78)	70.02	19.63	11.33	100.00
Clock drawing (n = 68)	8.25	4.93	.00	24.00
P(r)VLT (n = 83)	71.23	13.03	39.00	98.00
Fluency (n = 71)	0.52	0.14	0.10	1.00

Abbreviations: GDS = Geriatric Depression Scale; LA = leukoaraiosis; MMSE = Mini-Mental State Examination; proportion LA = total LA/total WM listed at 4 decimals to aid in percentage conversion; P(r)VLT = Philadelphia (repeatable) Verbal Learning Test; TICV = total intracranial volume; WM = white matter.

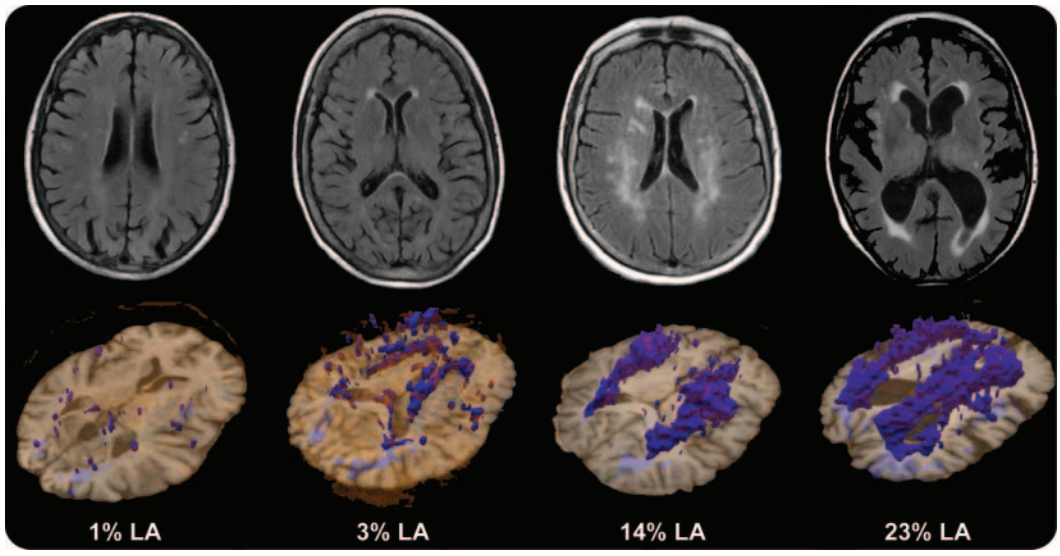
Statistical analysis. To investigate the adjusted relationships between each neuropsychological variable and each continuous LA Proportion variable, we used a regression spline approach, based on hypotheses that the relationships were smooth but possibly nonlinear. Specifically, each neuropsychological variable was regressed onto the LA Proportion variable using a 6-dimensional regression spline basis[32] with 2 interior knots and additionally adjusting for scaled and centered versions of the covariates age, education, MMSE score, total hippocampal, lacune, and intracranial volume. For Mental Control and Lexical Fluency Index, which are measured as proportions, a generalized linear model with a logit link and constant variance function was used.[32] For total clock errors, which are measured as a count, a log link and Poisson variance function was used. For the P(r)VLT recognition discrimination index, the identity link and constant variance function was employed. The predicted value of each outcome was graphed as a function of LA Proportion, at the mean value of the other covariates; 95% pointwise confidence intervals were included. χ^2 analysis of deviance test[32] was used to assess the statistical significance of LA Proportion (vs a constant) on the neuropsychological variables in the presence of the other covariates. Statistics reported the percent deviance explained.[32] The statistical language *R* version 2.11.1 (The R Foundation for Statistical Computing 2010[33]; http://www.r-project.org/) was used for these computations. Iterative hierarchical regressions then examined the amount of LA Proportion necessary to significantly contribute to cognitive performance after controlling for significant covariates. Results are reported as a percentage. For these regressions, covariates were entered first, followed by iterative amounts of LA Proportion (i.e., 0.01 entered in step 2 and then removed with this followed by entry of 0.02).

RESULTS

Demographics and volumetric variables. A series of 121 participants were originally included in the investigation with 38 excluded due to MRI scan quality or missing necessary sequences for segmentation programs (table). As a proportion to white matter as seen on MRI and measured with the semiautomated approach, LA ranged from 0.63% to 23.64% of the white matter (figure 1). A strong correlation between LA Proportion and the Junque LA Scale was obtained ($r = 0.74$, $p < 0.001$).

LA Proportion and neuropsychological test performance. For Mental Control, significant covariates were the MMSE score ($p < 0.001$) and bilateral hippocampal volume ($p = 0.02$), with LA Proportion significantly relating to performance (% deviance = 26.99; $p < 0.001$) (figure 2). For Clock Drawing errors, the MMSE ($p < 0.01$), age ($p < 0.001$), and hippocampal volume ($p = 0.04$) were significant covariates, with LA Proportion further significantly relating to performance (% deviance = 12.30, $p < 0.001$). Over that of MMSE, age, and a trend for hippocampal volume ($p = 0.06$), there was no relationship between LA Proportion and the P(r)VLT discrimination index or Lexical Fluency Index ($ps > 0.05$).

Figure 1 Increasing leukoaraiosis (LA) severity shown in traditional fluid-attenuated inversion recovery (FLAIR) slices and 3 dimensions



LA as a proportion to total white matter (1%, 3%, 14%, 23%) as measured by semiautomated approaches. Top row depicts percentages in traditional FLAIR view. Bottom row presents the same brain in a 3D view with the associated structural axial slice as a reference point (LA = blue; transparent orange = white matter).

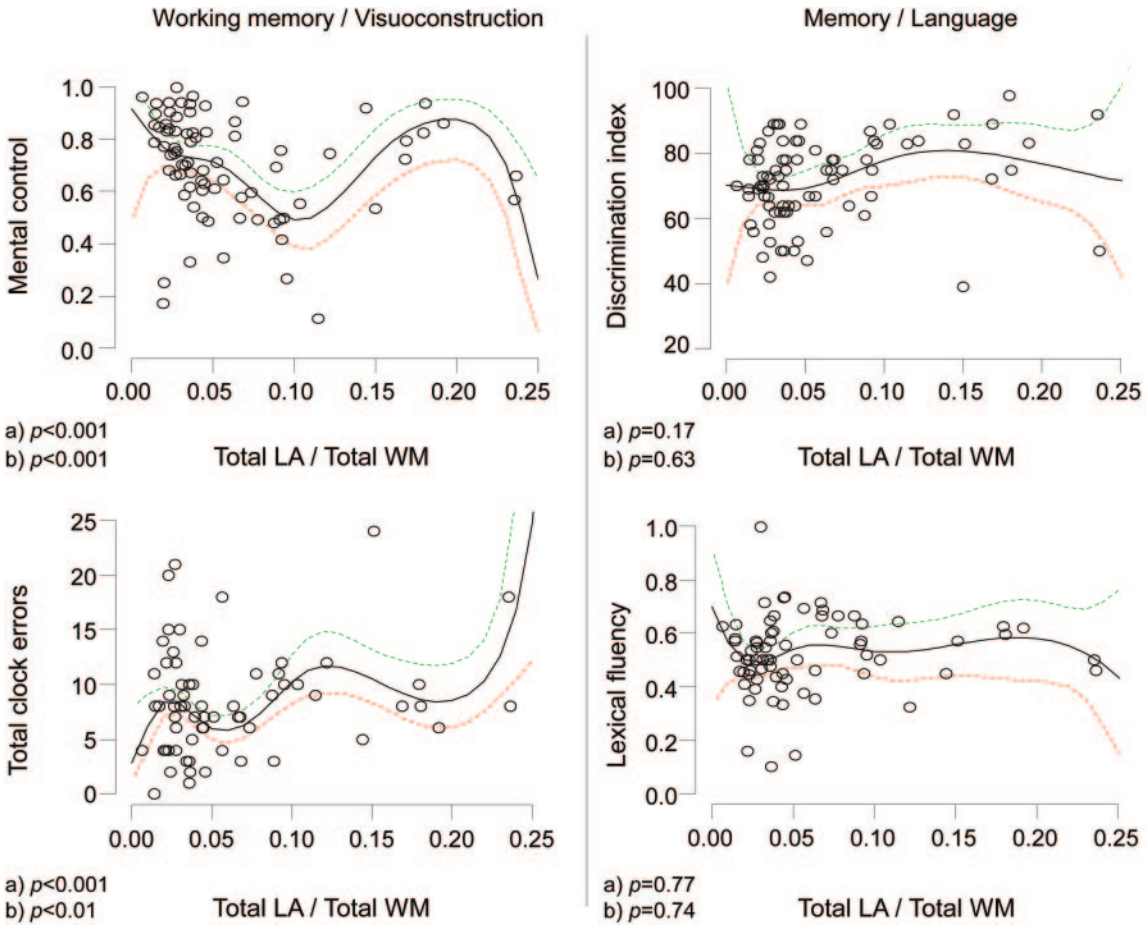
Linear vs nonlinear patterns. For the significant relationships reported above, nonlinear patterns were identified for Mental Control ($p < 0.001$) and Clock Drawing ($p < 0.01$). The P(r)VLT and Lexical Fluency Index relations to LA Proportion did not significantly differ from a linear association.

Threshold assessments: Executive function/working memory. At 0.03 indicating 3% of the white matter, LA proportion began to significantly add to the percent variance above that of MMSE and bilateral hippocampal volume ($R = 0.56$, adjusted $R^2 = 0.28$, $\beta = -0.28$, $p < 0.01$). LA Proportion of 3% corresponded with an average Mental Control score of 76.50 ± 16.58, which is near 2.0 standard deviations below normative values.[20] LA Proportion of 0.04 indicating 4% of the white matter was involved ($R = 0.61$, adjusted $R^2 = 0.37$, $\beta = -0.38$, $p < 0.001$) corresponded to an average Mental Control score of 65.78 ± 13.85, which is 3.0 standard deviations below normative values. Regression analyses continued to be statistically significant for every percentage point thereafter until Proportion LA reached 9% (for 5% to 8%, β range = −0.37 to −0.27, all p values <0.01; 9% $\beta = -0.17$, $p = 0.13$). For Clock Drawing, trends occurred for 13% and 14% of the white matter ($R = 0.27$, adjusted $R^2 = 0.10$, $\beta = 0.20$, $p = 0.09$). For the P(r)VLT and Lexical Fluency Index, there were no specific threshold points.

DISCUSSION A novel feature of this research is the volumetric assessment of LA as a proportion to white matter to examine the contribution of LA on cognition in dementia. In the current study sample of individuals with AD/VaD spectrum dementia, up to a quarter of white matter volume contained LA. Furthermore, a specific threshold of LA was associated with differential impairment on executive tests that assess working memory. Working memory scores (i.e., Mental Control) were significantly impaired when LA was present in 3% of the white matter. At this percentage, Mental Control scores were at nearly 2 standard deviations below that of published normative values. When LA was present in 5% of the total white matter, scores were more than 3 standard deviations below normative values. No additional impairment on mental control was observed when LA involved 9% or more of the white matter. Impaired performance on visuoconstruction (i.e., Clock Drawing), by contrast, may require as much as 13% of LA within the white matter. There were no LA threshold patterns for the memory or language measures thereby supporting hypotheses of their dependency upon posterior gray-white matter networks.[34]

A new finding from the current research was the curvilinear relationship between LA and executive functioning in dementia, such that additional LA involvement beyond a critical percentage did not contribute to any additional decrement in cognitive performance. The curvilinear relationships and corresponding thresholds were distinctly different for the 2 executive measures (i.e., Mental Control, Clock Drawing), again suggesting that these measures rely on different aspects of executive functions or that they are differentially compromised by LA in demen-

Figure 2 Relationship between neuropsychological measures and leukoaraiosis (LA) as a percentage of total white matter



The *p* values refer to (a) statistical significance for LA and cognitive variable; (b) significant deviation from linear trend.

tia. The Mental Control test requires mental rehearsal, attention, and inhibitory functions, including selective engagement and disengagement, as well as processing speed,[23,35] all of which have been associated with basal ganglia–frontal lobe network functions.[36] Intact connectivity between the frontal lobes and basal ganglia could be required for successful performance on this task. Therefore, it is not surprising that on this measure of working memory, patients with as little as 3% LA burden scored 2 standard deviations below published norms. The curvilinear pattern for Clock Drawing was less clearly demarcated by specific threshold points with potential inflection points of change suggested at higher LA burden levels (i.e., 13%). The reason for this dissociation may be related to the fact that successful clock drawing has been shown dependent upon a wide array of cognitive functions.[25,26] In addition to frontal-subcortical involvement, clock drawing requires visuospatial skills, operations dependent upon cortical gray matter involvement.[27,37] Clock drawing dependency on white matter integrity may be less crucial. This might also explain the nonexistent relationships between LA with episodic memory and language functions.

Among the patients with dementia studied, the amount of LA necessary for impairment in working memory or visuoconstructional ability was markedly less than the previously reported 25% thresholds based on visual rating scale.[4,5] The robust and significant correlation found between the semiautomated computer and Junque LA scale scores, however, suggests similar construct measurement. Quantifying LA as a proportion of white matter volume and head size corrects for individual variability and reveals more precise brain-cognitive associations in dementia.[7] Unlike visual ratings such as the Junque LA Scale,[6] which are based on a few select magnetic resonance slices in specified brain regions with limited data saving options (i.e., visual ratings are often recorded in writing), the magnetic resonance–derived semiautomated method quantified LA on every magnetic resonance slice, in all areas of the visible white matter, and allowed for measurement in binary computerized format, which will allow for future LA regional analyses. Advancing semiautomated programs

for clinical use in the future may be warranted. Until then, readers are encouraged to be mindful of the differences between visual rating tools and semiautomatic measurements and the impact of their differences on judgments of LA-cognitive associations.

The current research suggests LA severity informs us about the dominant form of cognitive impairment in patients with dementia. There are study limitations to consider, however. First, there are no pathology data and thus an analysis of LA differences in confirmed cases of "AD" vs subcortical "VaD" was not possible. All patients presented with an insidious onset of symptoms without conventional clinical features of multi-infarct dementia or de novo stroke. While in this sense the study sample is considered representative of patients commonly seen at memory clinics, study findings cannot be generalized to nondementia samples, those with numerous lacune or large strokes, or other disease states such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Additional research needs to be conducted to identify how LA may herald dementia onset in cognitively well and in distinct neurodegenerative samples. Second, the current study only examined total hemispheric LA rather than regional LA volumes. "Where" is often of greater importance than "how much." White matter fibers connect many polymodal and unimodal association cortical areas with the frontal lobes. These regions of the cerebral cortex have rich white matter connections with the limbic system and other brain regions.[38] Damage to selected pathways may differentially impair cognitive functions. There is some research suggesting that LA involving surface u-fibers may impact language abilities and that periventricular LA may impact memory and learning.[39] Additional studies on regional LA and the expression of dementia phenotypes are needed. Third, total LA only explained 20%–30% of the variance in working memory scores. Whereas LA is significantly associated with impaired working memory, this may be only one of many imaging biomarkers contributing to AD/VaD spectrum presentation. In dementia, the 3% threshold for working memory impairment may partially reflect a compromised cortex or basal ganglia, as well as alterations in neurotransmitter systems secondary to neurodegeneration. Finally, the role of non-LA white matter (i.e., "intact" white matter) on cognitive function was not examined. This white matter may harbor microstructural impairment not seen with traditional structural imaging approaches.[40] With all of these limitations in mind, the current study documents how subcortical white matter disease alters the phenotypic expression in insidious onset dementia syndromes.

AUTHOR CONTRIBUTIONS

Dr. Price: study concept, study supervision and coordination, data acquisition, analysis and interpretation, writing all drafts of manuscript, securing funding for study. Dr. Mitchell: study concept, data acquisition. Dr. Brumback: data analysis and revision of draft. J. Tanner: acquisition of data and revision of draft. Dr. Schmalfuss: study concept, data acquisition. Dr. Lamar: study concept, interpretation of data, revision of manuscript drafts. Dr. Giovannetti: study concept, interpretation of data, revision of manuscript drafts. Dr. Heilman: study concept, revision of draft. Dr. Libon: study concept, revision of draft, securing funding.

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DISCLOSURE

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