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ORIGINAL RESEARCH

Regional leukoaraiosis and cognition in non-demented older adults

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Abstract

Frontal lobe-executive functions are heavily dependent on distal white matter connectivity. Even with healthy aging there is an increase in leukoaraiosis that might interrupt this connectivity. The goal of this study is to learn 1) the location, depth, and percentage of leukoaraiosis in white matter among a sample of non-demented older adults and 2) associations between these leukoarioasis metrics and composites of cognitive efficiency (processing speed, working memory, and inhibitory function), and episodic memory. Participants were 154 non-demented older adults (age range 60–85) who completed a brain MRI and neuropsychological testing on the same day. Brain MRIs were segmented via Freesurfer and white matter leukoaraiosis depth segmentations was based on published criteria. On average, leukoaraiosis occupied 1 % of total white matter. There was no difference in LA distribution in the frontal (1.12%), parietal (1.10%), and occipital (0.95%) lobes; there was less LA load within the temporal lobe (0.23%). For cortical depth, leukoaraiosis was predominantly in the periventricular region (3.39%; deep 1.46%, infracortical 0.15%). Only increasing frontal lobe and periventricular leukoaraiosis were associated with a reduction in processing speed, working memory, and inhibitory function. Despite the general presence of LA throughout the brain, only frontal and periventricular LA contributed to the speeded and mental manipulation of executive functioning. This study provides a normative description of LA for non-demented adults to use as a comparison to more disease samples.

Keywords Brain aging · Hyperintensities · White matter alterations · Frontal lobes · Executive function · Episodic memory

Introduction

Leukoaraiosis (LA) represents signal intensity abnormalities in the cerebral white matter that can be seen on brain CT or MRI (Hachinski et al. 1986, 1987). LA occurs in approximately 15 to 65% of adults (Breteler et al. 1994; Liao et al. 1996; Lindgren et al. 1994; Schmidt et al. 1993; Schmidt et al. 1999; Tomimoto et al. 2006; Ylikoski et al. 1993). There is a threefold increase of LA in older adults relative to younger adults (Hogervorst et al. 2002). The cognitive relevance of LA in non-demented older adults remains controversial, even thirty years since its original description by Hachinski et al. (1986).

To date, the concept of *LA burden* (or the amount of LA needed to express specific phenotypic neurocognitive impairment) has focused on individuals with dementia. When LA is measured using visual rating scales such as the Junqué et al. (1990) scale, researchers show that a score of 10 on a 40 point

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scale (indicating 25% of the brain has LA), marks executive dysfunction as opposed to anterograde amnesia (Erkinjuntti et al. 2000; Libon et al. 2004; Price et al. 2012). In patients with dementia, this is a hallmark sign of greater executive and working memory deficits as opposed to episodic memory dysfunction (Lamar et al. 2009; Libon et al. 2008; Price et al. 2005; Price et al. 2012). When using a voxel-based method to calculate LA as a percentage of white matter (WM), executive dysfunction can occur with LA occupying as little as 3% of the white matter. Patients meeting any criteria for Alzheimer's Disease (AD) or subvascular dementia have, on average, LA in 6% of the WM (Price et al. 2012). A limitation of this research is the lack of a non-demented control sample. Prior research has exclusively used the Alzheimer's Disease Neuroimaging Initiative dataset (ADNI; www.loni.ucla.edu/ADNI) to assess patients diagnosed with mild cognitive impairment (MCI) without normal controls (Tosto et al. 2014; Tosto et al. 2015). It remains unknown how much LA occupies the cerebral white matter for non-demented healthy older adults.

Location of LA is another important concept, and although recent studies have pointed out parietal lobe LA in Alzheimer's disease, these studies did not compare region to cognitive profiles. Brickman et al. (2012) investigated severity and location of LA in individuals with Alzheimer's disease. From a sample of 503 non-demented older adults, Brickman et al. (2012) report that only parietal lobe LA predicts incident Alzheimer's disease such that for every 1-cm^3 increase in parietal lobe LA volume, there is a 19% increase in the risk of AD. In addition, Brickman et al. (2012) reported that parietal lobe LA appeared to be independent of hippocampal volume, suggesting LA is a distinct cerebrovascular marker for AD (Brickman et al. 2012). Lindemer et al. (2017) quantified the degree of LA in a sample classified as healthy older adults. This research included analyses of severity and spatial pattern of LA in participants with neurodegenerative diseases such as AD. In their sample of healthy older adults, LA was initially found in periventricular WM, as well as WM underlying the caudal and superior frontal, precuneus, and cingulum gray matter and then progressed to involve parietal, occipital, and medial temporal regions (Lindemer et al. 2017). Neither study, however, examined LA for specific cognitive profiles by lobe.

LA and cognitive profiles may be particularly important when we consider LA by "depth". LA is typically considered periventricular (surrounding the ventricles), but there is also LA within the deep white matter and immediately beneath the cortical gray matter (we call this 'infracortical' LA). LA may progress from periventricular to infracortical (deep LA) and proximal to the cortex (infracortical LA) (Lindemer et al. 2017; Spilt et al. 2006; Zimmerman et al. 1986), but this is still speculative. Differing pathologies may have distinct LA patterns. It is important we understand depth of LA in non-demented individuals for disease comparison purposes. Additionally, the cognitive contribution of LA in periventricular, deep, and infracortical regions remains unclear. Periventricular LA and cognition associations may relate to differences in how periventricular LA has been quantified (de Groot et al. 2000; Fukui et al. 1994; Ylikoski et al. 1993). LA that infiltrates the deep WM and surrounds the basal ganglia and thalamus hypothetically disrupts more cortical-subcortical connections, and particularly frontal-subcortical pathways necessary for rapid processing speed, working memory, and inhibitory function (Price et al. 2015; Lamar et al., 2009; Libon et al. 2004). Infracortical lesions, by contrast, may disrupt more u-fibers and associate with greater impairment in declarative and semantic memory, important in cognitive functions such as naming, reading, writing, calculating and copying figures (Stout et al. 1996).

In sum, although LA has been extensively studied in neurodegenerative disease, little is known about LA in those *without* dementia regarding (1) total LA burden, (2) severity of LA burden by lobe, (3) the depth of LA by lobe, (4) and how LA location might be associated with age-related decrements in neuropsychological functions. Given that LA accumulates with age, even in the absence of clinical evidence for dementia, it is important to investigate LA in non-demented individuals. Therefore, the present study provides normative information regarding LA in a cognitively healthy sample of older adults, including assessing the percentage of LA in white matter in each cortical lobe and the depth of LA (periventricular, deep, infracortical) and the possible relationships between the extent and location of LA and alterations in executive functions and episodic memory.

Methods

Standard protocol approvals, registrations, and patient consents

Participants were from a convenience sample of older adults age 60 and older who had enrolled in two separate federally funded investigations studying neuroimaging predictors of cognition. These participants were recruited through community advertisements and clinic outreach programs. Each participant signed a consent form approved by the University of Florida IRB and investigations followed the standards set forth in the Declaration of Helsinki.

Participants selected for the current study had to be non-demented, cognitively healthy individuals. All participants had to meet the following inclusion/exclusion criteria: 1) aged 60 or older, 2) English as primary language, 3) have intact activities of daily living (Lawton and Brody 1969), and 4) no signs of dementia based on neuropsychological testing. Two neuropsychologists reviewed cognitive data to confirm that test scores met the expected ranges for non-demented

individuals. Patients were excluded if there were any signs of a major neurocognitive disorder according to the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (American Psychiatric Association 2013). Additional exclusion criteria included: history of major depression, history of head trauma or neurodegenerative illness (e.g., Parkinson's disease), documented learning or seizure disorder, less than a sixth grade education, substance abuse in the last year, major cardiac disease, chronic medical illness known to induce encephalopathy (liver disease), history of major stroke, and implantable device precluding magnetic resonance imaging (MRI). A neuropsychologist or neuropsychology trained graduate student acquired this information via a structured background interview. Using a structured interview, a measurement of comorbidity was acquired (via the Charlson Comorbidity Index, CCI; Charlson et al. 1994). Current symptoms of depression were assessed with the Geriatric Depression Scale (Yesavage et al. 1982).

Brain MRI acquisition

Participants completed clinical brain MRI on a Siemens 3 Tesla Verio scanner using an 8-channel head coil. For WM analyses we acquired 1 T1-weighted scan (176 contiguous sagittal slices, $1mm^3$ voxels, 256×256 matrix, TR/TE = 2500/3.77 ms, 7/8 Partial Fourier, acquisition time 9:22). LA volumetrics were acquired from 3D fluid-attenuated inversion recovery (FLAIR) protocols (176 contiguous sagittal slices, $1mm^3$ voxels, 256×256 matrix, TR/TE = 6000/395 ms, acquisition time 8:50). Volume was calculated through the use of an algorithm for gap and slice thickness. All images were examined visually in order to determine excessive movement, and images displaying more than a moderate degree of movement were excluded.

Leukoaraiosis

A reliable rater trained by a neuroradiologist and with high spatial overlap (Dice Similarity Coefficient > .70) and high intra and inter-rater reliability for volume (>.90 ICC) measured all scans for LA within the supratentorial white matter using in-house macros for ImageJ (http://rsbweb.nih.gov/ij/docs/index.html). Measurements included periventricular caps and rims with semiautomated volumetric measures demonstrated to have criterion validity relative to the Junque LA Scale (Junqué et al. 1990). LA voxels for each brain slice were thresholded and created into 2D LA binary masks that were then concatenated into a 3D binary mask, providing an estimated total brain volume (mm^3). Mechanistically, the regions were delineated from T1 images. Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite version 6.0, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/; Fischl et al. 2002; Fischl 2012).

Imaging control variables

To control for head size variation, 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 with manual modifications performed by trained raters. The final variable was the estimated intracranial volume (mm^3).

Total LA volume

Total LA volume was computed by dividing the total LA volume for each participant by the total WM volume. Hemispheric LA volume was also calculated for combined left and right hemispheres, divided by total hemispheric volume.

LA lobe volume

General distribution of LA was assessed by acquiring the total LA volume for each lobe and dividing by total global LA volume. To assess the percentage of LA volume within the WM of each lobe, we divided LA volume by the WM volume of each lobe. These variables are referred to as frontal LA/WM, parietal LA/WM, temporal LA/WM, and occipital LA/WM.

LA depth (periventricular, deep, and infracortical) volume

Ventricle masks were dilated by 5 mm into white matter and then the original ventricle masks were subtracted from the dilated masks to create final periventricular masks. To create the infracortical region, the grey matter-white matter boundary of the cortex was identified by FreeSurfer and then inflated by 2 mm relative to every point along the boundary region of white matter. The deep region was delineated by subtracting the infracortical and periventricular masks from the entire prosencephalon white matter mask. Next, the FLAIR images were skull stripped using FSL BET (Jenkinson et al. 2012). The skull stripped FLAIR image was then co-registered with the FreeSurfer processed T1 image using FSL FLIRT (Jenkinson et al. 2002). The registration matrix was applied to LA masks, which were then segmented into three regional LA masks using *fslmaths*. To assess the percentage of LA volume within the WM of each region of depth, LA volume for each depth was divided by the WM volume for each depth. These variables are called periventricular LA/WM, deep LA/WM, and infracortical LA/WM.

Neuropsychological assessment

Participants first completed the Telephone Screening for Cognitive Status (TICS; Brandt et al. 1988) as part of the initial screening prior to the more thorough neuropsychological assessment. From the full neuropsychological assessment, we extracted information for two primary domains of interest: processing speed, working memory, inhibitory function (from this point forward called 'executive cognitive efficiency' to differentiate this subcomponent from the catch-all category of executive function which includes the more higher cortical gray matter domains of reasoning and abstraction) and episodic memory. Raw scores for individual tests were converted to z-scores using published age-corrected norms (Heaton et al. 2004; Wechsler 1997). Composite scores are average z-scores.

Executive cognitive efficiency (processing speed, working memory, inhibitory function)

Processing speed, working memory, and inhibitory function are cognitive functions that associate with white matter and frontal-subcortical integrity (Fuster 1985; Stuss 2011; Lezak et al. 2012). These are also foundational cognitive domains for executive function, with higher abstract reasoning associated with heteromodal association cortices that are more gray matter (Lezak et al. 2012).

Digit Symbol Coding (Wechsler 1997) from the Wechsler Adult Intelligence Scale –Third Edition (WAIS-III) was used as a measure of processing speed. This test requires participants to transpose a unique symbol with its corresponding number. Coding total score has been found to be sensitive to brain damage, even when lesion burden is minimal (Lezak et al. 2012). It is also one of the first tests to decline among patients with MCI and therefore is sensitive to the putative emergence of dementia (Devanand et al. 2007; Tabert et al. 2006). Dependent variable = total number of items completed in 120 s.

Digit Span Backward (Wechsler 1997) from the WAIS-III– considered a measure of working memory, has been shown to be associated with the dorsolateral prefrontal cortex and the frontal and parietal lobes (Amici et al. 2007; Leskelä et al. 1999). Dependent variable = total number of correct trials.

Trail Making Test, Part B minus Part A (Corrigan et al. 1987; Reitan 1958) involves visual scanning and inhibition. An inhibitory derivative was calculated by subtracting each participant's processing and visual scanning element of Trail Making Test, Part A, from the more inhibitory demanding test of Trail Making Test, Part B. This final score was used as a derived measure of inhibitory function correcting for processing speed limitations. Dependent variable = total completion time in seconds.

Episodic memory

The Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R; Brandt and Benedict 2001) is considered a measure of episodic memory. Episodic memory is associated with the rhinal cortex and hippocampus and is known to be reduced for individuals with memory impairment (Fernández et al. 1999). Furthermore, long-term delayed recall (20–30 min) associates with hippocampal volume (Wolk and Dickerson 2011). Dependent variable = total number of items recalled after a 20-min delay.

Logical Memory II Delayed Recall from the Wechsler Memory Scale – Third Edition (Wechsler 1997) is a measure of delayed recall. Dependent variable = the number of story components correctly recalled across both stories after a 30-min delay.

Statistical analyses

Regional lobe and depth LA

Left and right hemispheric LA volumes were compared using a paired samples t-test. LA/WM proportion variables were first compared through visual assessment of the histograms, followed by a statistical comparison using a related samples Wilcoxon signed ranks test to compare the medians due to the non-normality of the LA/WM distribution; we did not compare for intracranial volume as this is a within-person comparison. Paired samples t-tests with bootstrapping were also used to compare the means of the LA/WM proportion variables.

When we compared LA proportions across regions, we used a related samples Wilcoxon signed ranks test. We did not correct for intracranial volume as this is a within-participant comparison.

LA and cognitive domain associations

For assessing the association between LA proportions and cognition, we used linear regression with cognition as the outcome and natural log transformed LA/WM proportions (due to a skewed distribution), age, and intracranial volume as covariates.

Results

Participants

Table 1. From corpus of 160 participants from two federally funded investigations, we identified 6 participants who did not meet inclusion criteria. The final sample included 154 individuals with an average age of 68.97 years ranging from 60 to 85 years, split between male and female (53.4% male), and

Table 1 Participant demographics ($n = 154$)

	Mean	SD	Minimum	Maximum
Age (years)	68.97	5.77	60.00	85.00
Male: Female	83:71			
Education (years)	16.04	2.28	9.00	24.00
TICS Score ($n = 153$)*	37.81	3.46	30.00	47.00
Charlson Comorbidity Index	0.36	0.69	0.00	4.00

Note: * Baseline TICS score was missing for one participant

well educated (mean = 16.04 years). There was no statistically significant difference in LA between left and right hemispheres and so total from both hemispheres was used in all analyses. Total LA load ranged from 0.02 to 11.48% in our sample. Total LA percentage, LA by lobe, and LA depth did not associate with education, sex, GDS score, or TICS score.

LA by lobe (frontal, parietal, occipital, temporal)

Histogram data are shown in Supplemental Fig. 1.

Table 2, Figs. 1 and 2. A related samples Wilcoxon signed ranks test showed that frontal lobe LA/WM was significantly greater than parietal lobe LA/WM (frontal lobe median = .0065, parietal lobe median = .0033; $p < .001$) and temporal lobe LA/WM (temporal lobe median = .0009; $p < .001$). However, there was no difference between frontal and occipital lobe LA (occipital lobe median = .0070; $p > .05$). This non-significant finding is due to a significant difference in the means, but not the medians, of frontal and occipital LA/WM. A paired-samples t-test with bootstrapping was conducted as a post-hoc analysis, which demonstrated greater frontal lobe LA/WM volume than occipital lobe LA/WM volume (frontal LA/WM mean = .0112, occipital LA/WM mean = .0095; $p < .05$). When using the paired samples t-test with bootstrapping to compare frontal and parietal LA/WM volumes, there was no significant difference ($p > .05$). Therefore, assessing the means and the medians of lobe LA/WM resulted in different findings. Taken together, these collective findings indicate no differential distribution of LA/WM by lobe in the frontal, parietal, and occipital regions. The temporal lobe had less LA/WM than the frontal, parietal or occipital lobes.

Depth of LA (periventricular, deep, infracortical)

Histogram data are shown in Supplemental Fig. 2.

Table 3, Fig. 3. When comparing LA depth using related samples Wilcoxon signed ranks tests, periventricular LA/WM proportion was significantly greater than deep LA/WM proportion (periventricular LA/WM median = .0212, deep LA/WM median = .0032; $p < .001$) and infracortical LA proportion (infracortical LA/WM median = .0006; $p < .001$). Post-hoc analyses using paired samples t-tests with bootstrapping confirmed these findings (all $p < .05$).

LA lobe / depth and composites

Lobe LA and executive/memory composites

Only frontal lobe LA/WM negatively associated with the executive cognitive efficiency composite ($\beta = -.19$; $t(153) = -2.20$, $p < .05$; effect size of 0.2). There was no statistically significant relationship between any lobe LA/WM and episodic memory in our non-demented sample of older adults.

Depth of LA and executive/memory composites

Only periventricular LA/WM negatively associated with executive cognitive efficiency composite ($\beta = -.19$; $t(153) = -2.30$, $p < .05$, effect size = 0.2). There were no statistically significant relationships between LA/WM depths and episodic memory.

Discussion

Although all individuals presented with some LA, most (71%) had LA in less than 1 % of their white matter. This finding is in contrast to Price et al. (2012) who reported that dementia populations contained an average of 6% of LA in their white

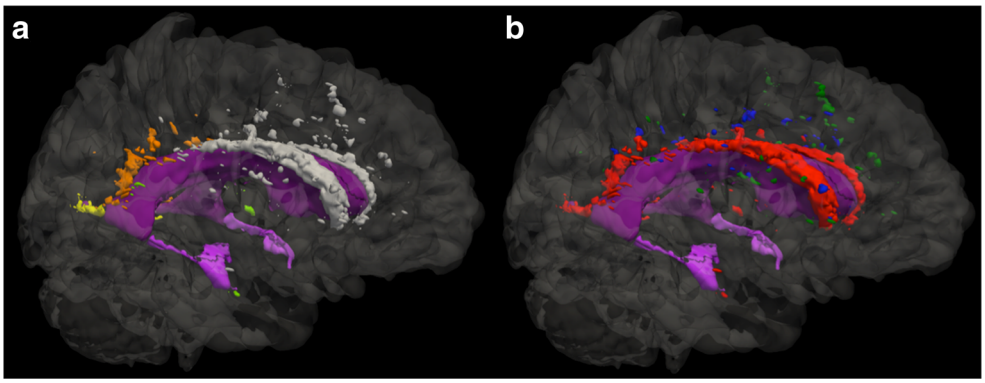

Fig. 1 Representative participant brain with the ventricle (purple) and leukoaraosis segmented by LOBE (Fig. 1a): Frontal (gray); Parietal (orange), Occipital (yellow), Temporal (green); and DEPTH (Fig. 1b): Periventricular (red), Deep (green), Infracortical (blue)

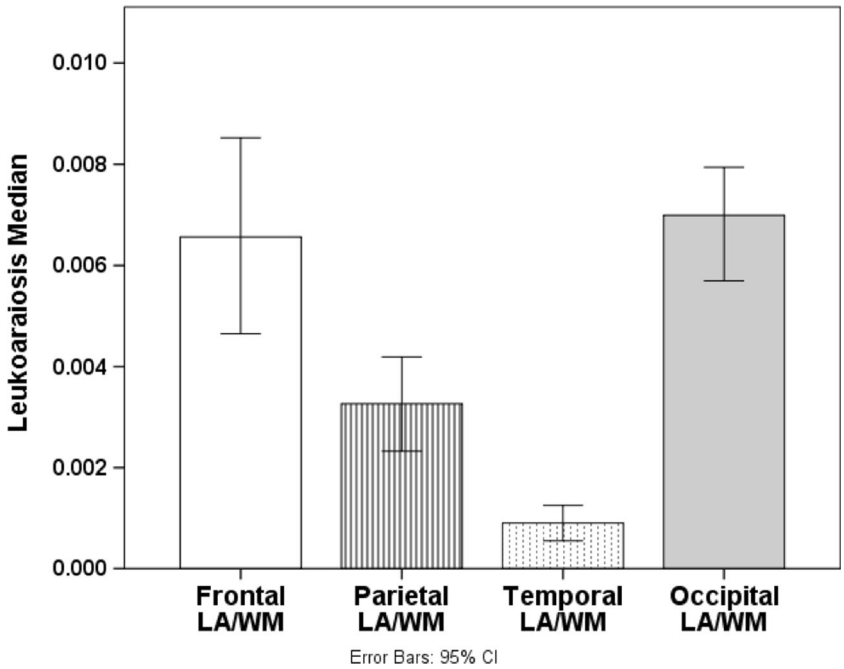

Fig. 2 Median leukoaraiosis (LA) by lobe

matter, and that a minimum of 3% explained variance in working memory performance. In this study, only 7 of our 155 participants had LA in more than 3% percent of their WM. Furthermore, there was no differential distribution of LA in the frontal, parietal, and occipital regions in the present sample. These findings complement Brickman et al.' (2012) dementia-focused investigations demonstrating that individuals with AD pathology showed LA predominantly within the parietal region. We did not observe any LA regional associations with memory function. Rather, frontal and periventricular LA were negatively associated with a reduction in an executive cognitive efficiency composite consisting of working memory, processing speed, and inhibitory function.

Regarding lobe and depth location, LA in our non-demented sample was predominantly in the frontal, parietal, and occipital lobes, largely absent in the temporal lobe, and in regard to depth was predominantly in the periventricular region. There was little to no LA in the deep or infracortical regions. Moreover, only frontal and periventricular LA load negatively associated (albeit mildly) with executive cognitive efficiency scores. LA did not associate with delayed episodic memory performance. These findings reiterate the importance of frontal white matter and periventricular white matter regions on the supportive system of executive functioning – namely processing speed, working memory, and inhibitory function. Although the frontal lobe is the largest lobe in the human brain, it remains the most vulnerable to white matter burden. Indeed, loss of white matter occurs earlier than gray matter (Michielse et al. 2010). Given the involvement of the periventricular regions, we speculate that fibers extending from the dorsomedial nucleus of the thalamus may be disrupted (Van der Werf et al. 2003), for these connections traverse the white matter areas altered by periventricular and frontal white matter regions.

Individuals with dementia and other pathologies, however, should have LA in different regions, depending on pathology. Price et al. (2015) examined patients with AD and vascular dementia (VaD), dividing the patient groups into single domain amnestic, single domain dysexecutive, and multi-domain phenotypes. They found that the dysexecutive and multi-domain groups had greater amounts of LA in the deep and periventricular regions of the brain than the amnestic group, however there were no between-group differences in infracortical LA (Price et al. 2015). Furthermore, greater LA

Table 2 Mean, standard deviation, and minimum, maximum values for Leukoariosis (LA) volume by lobe (n = 154)

	Frontal	Temporal	Parietal	Occipital	Total
Raw mm^3	2460.94 ± 3208.388	154.05 ± 327.71	1092.21 ± 2387.88	381.64 ± 399.53	4125.38 ± 6056.77
Min, Max	62.00, 23,158.00	1.00, 3297.00	1.00, 17,947.00	1.00, 2714.00	108.00, 46,261.00
%WM*	1.12 ± 1.51	0.23 ± 0.52	1.10 ± 2.38	0.95 ± 0.99	0.97 ± 1.45
Min, Max	0.03, 11.33	0.00, 5.34	0.00, 18.00	0.00, 6.00	0.02, 11.48

*%WM = (Raw lobe LA/Raw lobe WM Volume for lobe)×100; (Raw Total LA/Raw Total Volume for total)×100

Table 3 Leukoaraiosis (LA) Volume by Depth (Periventricular, Deep, Infracortical; n = 154)

	Periventricular	Deep	Infracortical	Total
Raw mm^3	3023.26 ± 3863.59	664.10 ± 1647.78	438.02 ± 820.60	4125.38 ± 6056.77
Min, Max	70.00, 29,264.00	0.00, 12,601.00	0.00, 7379.00	108.00, 46,261.00
%WM*	3.41 ± 3.89	1.47 ± 4.01	0.15 ± 0.29	0.97 ± 1.45
Min, Max	0.08, 30.41	0.00, 33.34	0.00, 2.59	0.02, 11.48

*%WM = (Raw Region LA/Raw Region WM Volume)×100

load in the dysexecutive and multi-domain groups was associated with a reduced caudate nuclei volume, suggesting compromised frontal-subcortical networks (Price et al. 2015). This between-group difference may also be due to vasculature of the brain. Fibers from the frontal lobe to the striatum initially travel alongside long association fibers within the frontal-occipital fasciculus, later separating with some fibers ending in the caudate nucleus and putamen. Another group of fibers from the striatum enters the external capsule, later targeting the caudate nucleus, putamen, and claustrum. Therefore, greater amounts of LA in the periventricular and deep brain regions could disrupt function of the caudate nucleus. LA in the deep regions rather than periventricular region alone may be hallmark signs of vascular dementia presence. It is unknown where LA is most prevalent for other disorders such as atrial fibrillation or other vascular risk factors. These studies are needed.

We recognize study limitations and have suggestions for future research investigations. We focused on our study on non-demented adults and this classification included possible mild cognitive impairment. To address concerns about mild cognitive impairment, we used the Jak et al. (2009) comprehensive criteria to retrospectively classify participants with mild cognitive impairment. Of our 154 participants, 18 met comprehensive criteria. MCI and non-MCI participants did not differ in any lobe or region of LA. We encourage future researchers to examine LA by region and depth in larger and diverse samples of MCI relative to cognitively "well" individuals. We also encourage researchers to examine other domains of cognitive abilities, such as visuospatial attention, by region and lobe of LA in MCI and non-MCI individuals. Other considerations include comorbidity. A third of our sample reported a diagnosis of type II diabetes, but this could not be confirmed with medical records. Although our post-hoc analysis of LA load for patents with high versus low comorbidity did not show a difference in LA load or region, we recognize it as a limitation given research showing higher rates of LA for individuals with longer diabetes disease duration (Del Bene et al. 2015). We did not control for vitamin D, and this too has ben shown to be involved with greater periventricular LA (Annweiler et al. 2014). Future studies are also encouraged to examine more diverse racial/ethnic samples, as well as individuals with depressive symptoms (see Wang et al. 2014); our findings are only applicable to Caucasians who are well-educated and reporting few symptoms of depression.

Despite these limitations, the study has many strengths. We expanded on the concept of regional LA relative to cognition

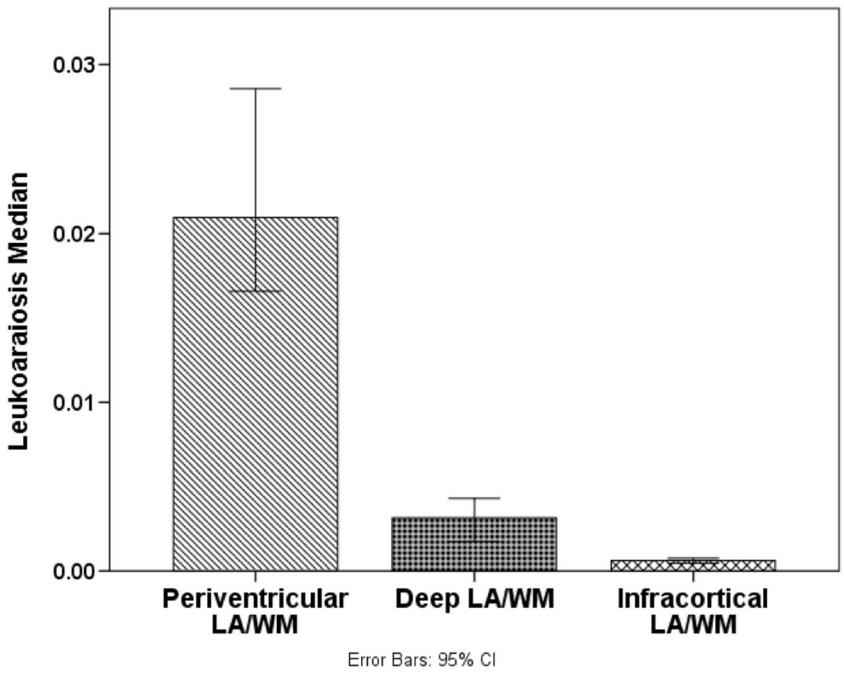

Fig. 3 Median leukoaraiosis (LA) by depth

using infracortical and deep definitions that are grounded in our understanding of white matter structure (long intrahemispheric fibers, frontal-subcortical fibers, u-fibers near the cortex). We quantified LA by lobe and depth correcting for white matter thereby providing a percentage that can be clinically meaningful relative to other disease samples. These data provide insight into the typical age-related accumulation of LA, thereby providing a comparison reference for LA in patients with other comorbidities.

LA is an infiltrating change to the white matter that needs close examination using sophisticated neuroimaging measurement approaches but also clinically behaviorally relevant variables. The current study adds to the body of literature showing that LA is not a benign entity, even in non-demented adults.

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Compliance with ethical standards

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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