

Associations Of Lobar, Periventricular And Deep White Matter Hyperintensities With Age-related Neuropathologies

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Gulam Mahfuz Chowdhury¹, Khalid Saifullah¹, Abdur Raquib Ridwan², Md Tahmid Yasar¹, Julie A. Schneider², Konstantinos Arfanakis^{1,2}

¹Illinois Institute of Technology, Chicago, IL, USA

²Rush University Medical Center, Chicago, IL, USA



Introduction

Brain white matter hyperintensities (WMH) appear bright on T2-weighted MRI scans¹ and are common in older adults², increase in volume with age, cardiovascular risk factors, and cerebral small vessel diseases³. Furthermore, WMH have been associated with cognitive and motor decline, and Alzheimer's dementia⁴. However, the neuropathologies associated with WMH in different parts of the brain are not well understood. This study combined ex-vivo MRI with detailed neuropathologic examination in a large group of community-based older adults to quantify WMH volumes in different periventricular and deep brain regions and examine the association of regional WMH volume with age-related neuropathologies.

Methods

Participants, MRI, neuropathologic examination:

This work included 773 older adults participating in four longitudinal clinical-pathologic cohort studies of aging, Rush MAP⁵, ROS, MARS⁶, and Clinical Core of the Rush ADRC. All participants underwent autopsy. Cerebral hemispheres from all participants were imaged ex-vivo on 3T clinical MRI scanners approximately one month postmortem. WMH were segmented automatically using an in-house approach. All hemispheres were segmented into frontal, parietal, occipital, temporal, and subcortical areas using multi-atlas segmentation⁷. Ventricles and gray matter were segmented in an ex-vivo cerebral hemisphere template and were expanded by 5, 6, 7, 8, 9, or 10 mm (avoiding overlap) to define periventricular and juxtacortical regions. The template was then registered to each individual hemisphere, and the transformations were used to transfer the periventricular mask to each participant's native space. The portion of each hemisphere not included in the periventricular mask was considered as deep tissue. WMH volumes were then calculated for the 10 regions (periventricular and deep frontal, parietal, occipital, temporal, and subcortical), were normalized by the participant's total hemisphere volume, and multiplied by 1000.

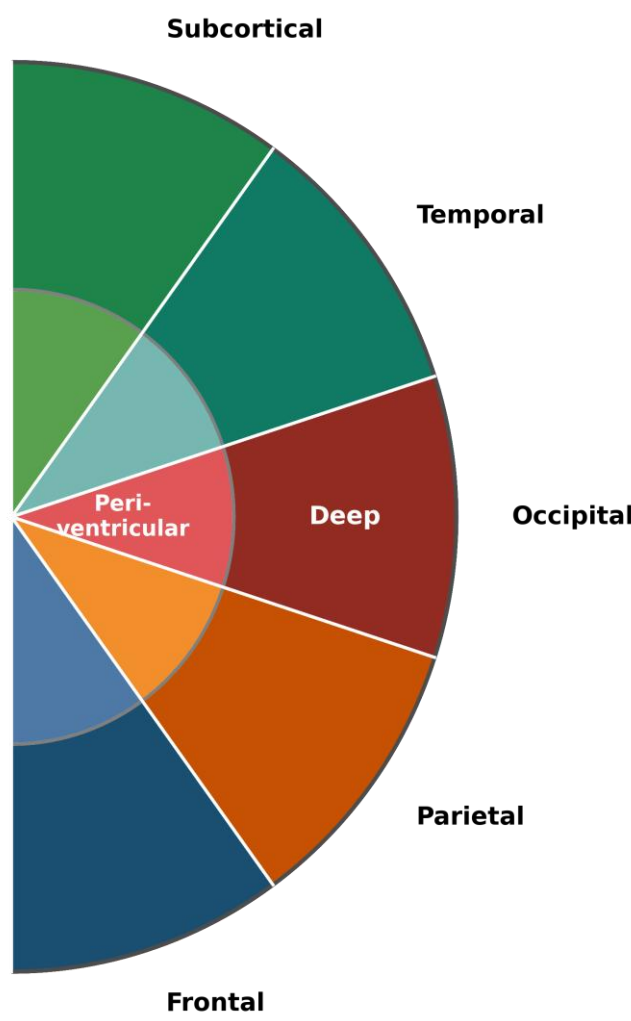


Fig. 1: Ten brain regions

Following ex-vivo MRI, all hemispheres underwent detailed neuropathologic examination. The assessed pathologies included atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy (CAA), gross and microscopic infarcts, amyloid- β plaques, neurofibrillary tangles, Lewy bodies, and limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) (Table 2).

Demographics and Neuropathologic Characteristics

Characteristics		Characteristics	
N	773	Atherosclerosis, n (%)	
Age at death, y (SD)	90.6 (6.4)	None or mild	583 (75.4)
Male, n (%)	211 (27.3)	Moderate or severe	190 (24.6)
Education, y (SD)	16.4 (3.6)	Arteriolosclerosis, n (%)	
Antemortem clinical diagnosis		None or mild	571 (73.9)
No cognitive impairment	239 (30.9)	Moderate or severe	202 (26.1)
Mild cognitive impairment	179 (23.2)	Cerebral amyloid angiopathy, n (%)	
Dementia	355 (45.9)	None or mild	498 (64.4)
Mini-Mental State Examination (MMSE), mean (SD)	19.8 (9.6)	Moderate or severe	275 (35.6)
At least one copy of the $\epsilon 4$ allele, n (%)	198 (25.6)	Gross infarcts, n (%)	314 (40.6)
Postmortem interval to fixation, h (SD)	9.5 (6.7)	Microscopic infarcts, n (%)	302 (39.1)
Postmortem interval to imaging, d (SD)	37.3 (17.1)	AD-NC (NIA-AA criteria), n (%)	
Heart Disease, n (%)	152 (19.7)	None or low	235 (30.4)
Hypertension, n (%)	552 (71.4)	Intermediate or high	538 (69.6)
Diabetes, n (%)	187 (24.2)	Lewy bodies, n (%)	227 (29.4)
Smoking, n (%)	259 (33.5)	LATE-NC, n (%)	
		(stage 0/1) no TDP-43 inclusion or inclusions in amygdala	476 (61.6)
		(stage 2/3) TDP-43 inclusions in amygdala and entorhinal cortex, hippocampus or neocortex	297 (38.4)

Table.1: Demographic and clinical characteristics of the participants

Table.2: Neuropathologic characteristics

Results

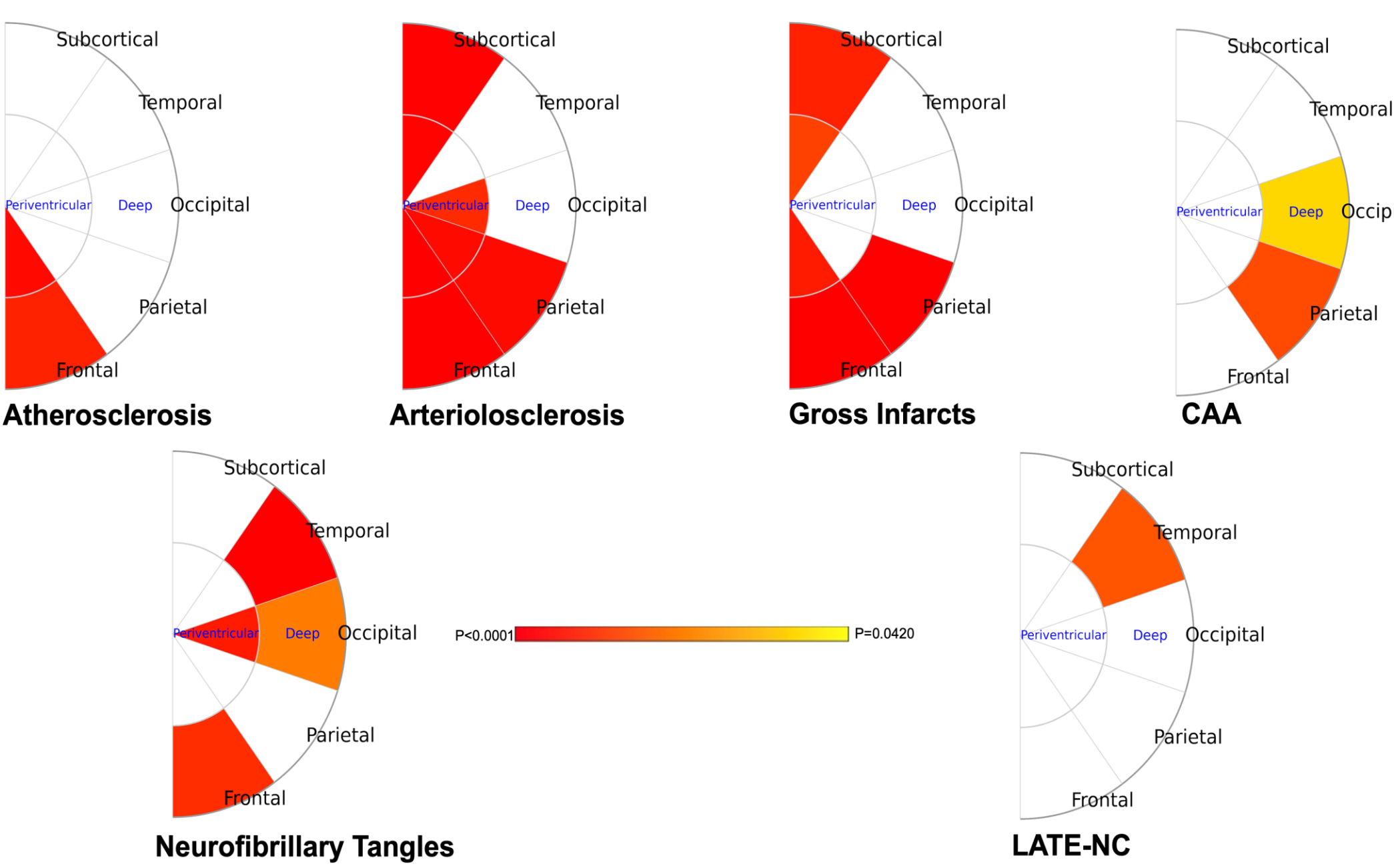


Fig. 2: Associations of WMH with neuropathologies in different brain regions

Statistical Analyses

Linear regression was used to test the association of regional WMH volume (dependent variable) with age-related neuropathologies (included in the same linear regression model), controlling for age at death, sex, education, scanner, postmortem intervals to fixation and to imaging (Table 1). The FSL PALM⁸ tool with 10,000 permutations and tail acceleration was used for the statistical analysis. Associations were considered significant at $p < 0.05$ after family-wise error rate (FWER) correction for multiple comparisons.

Discussion

This study shows detailed WMH patterns associated with different age-related neuropathologies in community-based older adults. Similar results were obtained when defining the periventricular region in the hemisphere template at different distances from 5 to 10mm from the ventricles. Atherosclerosis, arteriolosclerosis, neurofibrillary tangles, gross infarcts, and cerebral amyloid angiopathy showed associations with WMH volume in different periventricular and deep brain regions.

Both vascular and neurodegenerative pathologies were associated with regional WMH volumes. Substantial differences exist in WMH patterns across different neuropathologies. Periventricular WMH were mostly associated with vascular pathologies, while deep WMH were associated with both vascular and neurodegenerative pathologies. Vascular pathologies like arteriolosclerosis and gross infarcts were linked to greater WMH volumes in most brain regions, while CAA showed association only in posterior portions of the brain, and in particular deep tissue (not periventricular) which is in line with the fact that CAA affects cortical and leptomeningeal vessels. Neurofibrillary tangles and LATE-NC were associated with WMH particularly in the temporal and frontal lobes where the two pathologies are known to have a high impact.

Conclusion

This study combined ex-vivo MRI and detailed neuropathological examination in a large sample of community-based older adults and showed detailed patterns of WMH associated with different age-related neuropathologies.

References:

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Correspondence to: Konstantinos Arfanakis, arfanakis@illinoistech.edu