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White Matter Hyperintensity Spatial Patterns Provide Clues About Underlying Disease: Location Matters!

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Handling Editor Statement:

White matter hyperintensities (WMH) of presumed vascular origin are the most widely studied manifestations of cerebral small vessel disease on brain MRI.[1] Despite the growing body of literature on the imaging characteristics, spatial and temporal trajectories, as well as clinical correlates of WMH, there remain considerable unknowns regarding their underlying pathophysiology.[2] Indeed, insights from radiological-histological correlation studies have underscored the heterogeneous nature of WMH pathology, which seems to differ by brain region studied.[3] Multiple approaches have been proposed to further investigate the spatial patterns in which WMH present and determine their association with disease and risk factors. These are often either hypothesis-driven, e.g. by differentiating WMH based on their underlying vascular territory[4], or data-driven using more localized, voxel-wise approaches[5]. As such, there has been an unmet need for established data-driven approaches to assess global topological patterns of WMH on brain MRI.

With the advent of deep learning enabled WMH segmentation algorithms, large scale data driven analyses into the underlying topology have become feasible using additional machine learning based clustering approaches. Nonetheless, the application of these methods to highly non-isotropic resolution images - which are often used in a clinical setting - can be challenging. U-Net style deep learning architectures, however, have proven to be able to address these challenges at different levels of image resolution and image quality.[6,7]

In this issue of *Neurology*, Phuah et al.[8] report findings from a multivariate voxel-based spectral clustering approach to identify different WMH spatial patterns on 3 tesla FLAIR MRI scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which were segmented using a U-Net style deep learning approach. The authors used scans from >1,000 participants and found five distinct WMH spatial patterns that reflected different underlying disease etiologies. Notably, a juxtacortical WMH pattern was associated with probable cerebral amyloid angiopathy (CAA) and increased accumulation of amyloid-β in the brain, whereas a deep frontal WMH pattern was

indicative of arteriolosclerosis. This work provides a much needed first step in the direction of exploring disease-specific spatially distinct patterns of WMH and opens the door to apply these types of data-driven approaches to other MRI manifestations of cerebral small vessel disease.

While this work provides an important step in the global data-driven analyses of spatial WMH patterns, there remain several challenges that should be addressed in future studies. Segmentations based on deep learning approaches are known to be biased towards the population on which they were trained. With a limited number of training and testing samples, and without an external validation set, it remains to be determined whether the algorithm developed by the authors will generalize to other studies. As such, reproducibility remains to be demonstrated in independent cohorts. In addition, as the challenge of accurately segmenting lesions on MRI with highly non-isotropic resolution remains, poor segmentation accuracy can lead to missed patterns or spurious signals in these kinds of analyses, which may benefit from the use of 3D FLAIR images. It therefore is crucial with any type of machine learning algorithm to tie findings back to specific, biologically plausible signals in the data. This also relates to clustering algorithms that are not necessarily producing stable results, e.g. due to different initialization of parameters, depending on a subset of the data. While juxtacortical WMH signals in ADNI have been reported previously using T1-weighted MRI scans[9], analyses need to take contrast specific signals that may not reflect the disease burden of interest, such as potential susceptibility artifacts, hyperintensities of the gray/white matter boundary, or enlarged perivascular spaces into account, as they may alter the findings. Especially in patients with CAA, MRI-visible perivascular spaces are often found in juxtacortical areas, with similar signal characteristics as WMH on FLAIR.[10]

Despite these potential caveats, establishing the existence of distinct spatial patterns of WMH will contribute to further our understanding on the underlying pathophysiological mechanisms that drive WMH in the first place. It further supports our understanding that WMH burden

develops heterogeneously throughout the brain and that other aspects besides known risk factors are highly relevant to these observed patterns. Notably, as topological differences in WMH are becoming of great interest to the community, the study highlights the importance of accounting for other comorbidities in the process. This is of particular importance for the translation of these findings into clinically-relevant biomarkers of disease state and trajectories.

In conclusion, while WMH have traditionally been regarded as the hallmark signs of cerebral small vessel disease, the recent push to unravel their distinct topological patterns holds the potential to better understand underlying mechanisms that give rise to WMH, which includes an amyloid-related pathophysiology. As such, incorporating WMH spatial patterns may contribute to improved clinical decision making in the future. The remaining questions of reproducibility and generalizability will need to be addressed in large-scale analyses beyond the populations presented in this study to ensure its utility for clinical use.

References

[1] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013 Aug;12(8):822-38.

[2] Alber J, Alladi S, Bae HJ, Barton DA, Beckett LA, Bell JM, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. *Alzheimers Dement (N Y)*. 2019 Apr 9;5:107-117.

[3] van Veluw SJ, Arfanakis K, Schneider JA. Neuropathology of Vascular Brain Health: Insights From Ex Vivo Magnetic Resonance Imaging-Histopathology Studies in Cerebral Small Vessel Disease. *Stroke*. 2022 Feb;53(2):404-415.

[4] Schirmer MD, Giese AK, Fotiadis P, Etherton MR, Cloonan L, Viswanathan A, et al. Spatial Signature of White Matter Hyperintensities in Stroke Patients. *Front Neurol.* 2019 Mar 19;10:208.

[5] Rostrup E, Gouw AA, Vrenken H, van Straaten EC, Ropele S, Pantoni L, et al. The spatial distribution of age-related white matter changes as a function of vascular risk factors--results from the LADIS study. *Neuroimage.* 2012 Apr 15;60(3):1597-607.

[6] Kuijf HJ, Biesbroek JM, De Bresser J, Heinen R, Andermatt S, Bento M, et al. Standardized Assessment of Automatic Segmentation of White Matter Hyperintensities and Results of the WMH Segmentation Challenge. *IEEE Trans Med Imaging.* 2019 Nov;38(11):2556-2568.

[7] Schirmer MD, Dalca AV, Sridharan R, Giese AK, Donahue KL, Nardin MJ, et al. White matter hyperintensity quantification in large-scale clinical acute ischemic stroke cohorts - The MRI-GENIE study. *Neuroimage Clin.* 2019;23:101884.

[8] Phuah C, Chen Y, Strain JF, Yechoor N, Laurido-Soto OJ, Ances BM, Lee J. Association of data-driven white matter hyperintensity spatial signatures with distinct cerebral small vessel disease etiologies. *Neurology* 2022;XX:xx-xx.

[9] Lindemer ER, Greve DN, Fischl B, Augustinack JC, Salat DH; Alzheimer's Disease Neuroimaging Initiative. Differential Regional Distribution of Juxtacortical White Matter Signal Abnormalities in Aging and Alzheimer's Disease. *J Alzheimers Dis.* 2017;57(1):293-303.

[10] Perosa V, Oltmer J, Munting LP, Freeze WM, Auger CA, Scherlek AA, et al. Perivascular space dilation is associated with vascular amyloid-β accumulation in the overlying cortex. *Acta Neuropathol.* 2022 Mar;143(3):331-348.

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