Shades of White
Separating Degrees of Injury in the Aging Brain
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See related article, p XXX.

In the play Art by Yasmina Reza, the main character puts his friendship with 2 others at risk when he purchases a piece of modern art that consists of a large white canvas with barely visible fine diagonal white lines.1 One of his friends attempts to explain the work to the unconvinced third.

"Imagine a canvas about five foot by four…with a white background…completely white in fact…with fine white diagonal stripes…""

"If the background’s white, how can you see the lines?" his friend asks.

"You just do….or anyway there are degrees of white! There’s more than one kind of white!" he responds, exasperated.

In this issue of Stroke, Maillard et al2 quantitatively define the different types of white in the aging brain by examining fluid attenuation inversion recovery (FLAIR) intensity maps and fractional anisotropy (FA) in regions of white matter hyperintensities (WMH) and surrounding tissue. This work nicely elaborates and extends early work on diffusion changes in normal-appearing white matter in genetic small vessel disease3 and previous work from this group in mild cognitive impairment and Alzheimer disease.4,5

WMH are frequently noted on FLAIR sequences in elderly patients. The prevalence of WMH increases with age6 and is associated with known vascular risk factors.7,8 The extent of WMH has been linked to cognitive impairment9 and to the risk of incident dementia.10 Progression of WMH has been associated with vascular risk factors in population-based studies.11,12 Treatments to prevent evolution or increase of white matter injury, such as adequate antihypertensive therapy,13 could be a critical intervention to reduce cognitive impairment in the elderly.

However, WMH are pathologically heterogeneous, ranging from subtle matrix alterations to severe axonal and myelin loss and may be related to one of a variety of different mechanisms.14 Better neuroimaging-based characterization of white matter injury is needed to understand how differing degrees of white matter injury develop and evolve in the elderly. This could lead to the development of therapeutic strategies to target types of white matter injury most implicated in cognitive impairment.

Although FLAIR imaging has been used widely in studies to identify areas of white matter injury, diffusion tensor imaging has been shown to be a more sensitive indicator of subtle white matter damage that may be associated with cognitive impairment.15,16 Although both FLAIR and diffusion tensor imaging have been shown to be predictors of future white matter damage,5 most studies to date have not explored these associations in detail. Most prior studies involving FLAIR have focused on WMH defined by specific intensity thresholds and have not used the full range of FLAIR intensity values. This consequently results in a binary distinction as to whether WMH are present or absent. Although continuous diffusion tensor imaging measures have been more frequently used to understand mechanisms of vascular cognitive impairment,16,17 cautious interpretation may be required because changes in diffusion measures depend not only on white matter damage but also on axonal fiber orientations and thus may be location dependent.

Maillard et al18 sought to understand how areas of severe white matter damage (WMH) and surrounding, more mildly damaged areas (which they term penumbra) evolve over time in 115 cognitively normal community-dwelling individuals. They sought to determine whether different types of WMH differed in their vulnerability to future white matter damage.

To accomplish this, they categorized WMH into 3 categories with their associated penumbra: (1) WMH that did not become larger on follow-up (stagnant WMH), (2) WMH that became larger on follow-up (growing WMH), and (3) WMH that were only identified on follow-up scans (noncontiguous incident WMH). Based on their previous work, penumbra was defined as white matter voxels within 8 mm of a WMH.18 Using established processing techniques, the investigators were able to generate normalized FLAIR and FA maps at baseline and follow-up (nFL and nFA, respectively).

Although growing WMH represented the largest volume of white matter lesion (3.44 cm3), stagnant WMH were considerable (0.85 cm3). By contrast, incident WMH represented the smallest volume of white matter lesion (0.32 cm3). In growing WMH, nFA values were lower (indicating more microstructural damage) than nFA values in stagnant or noncontiguous incident WMH. Similarly, mean nFL within growing WMH was greater (indicating more microstructural damage) compared with stagnant or noncontiguous incident WMH. However, in contrast to mean nFA, growing lesions did not show significant changes in nFL at follow-up. Interestingly, stagnant WMH areas showed a decrease in nFL between baseline and follow-up, which would suggest that these lesions are somehow improving (despite continued decrease in nFA).

For penumbra areas, nFA values were lower in growing WMH regions compared with stagnant or noncontiguous incident WMH penumbra regions. Similarly, nFL was significantly greater in penumbra surrounding growing WMH areas.
compared with the other 2 categories. Penumbra of growing WMH and penumbra of noncontiguous incident WMH showed increased nFL at follow-up. Finally, all WMH areas and their associated penumbra showed increase in microstructural damage over time as measured by nFA.

These interesting results show that not all WMH reflect the same degree of white matter damage and that there may be considerable heterogeneity in pathology between different WMH areas. The results further suggest that not all WMH share the same fate. This builds on and extends previous work in the literature.\(^2,9,20\) Furthermore, these results convincingly demonstrate that although diffusion tensor imaging–based measures could be used as a continuous measure of white matter integrity, FLAIR signal changes may have more of a plateau effect in more severely damaged white matter areas and may represent a more dichotomous measure.

This innovative study generates new questions to be addressed about WMH. As the authors were only able to examine 2 time points in this study, future studies may wish to address whether white matter integrity decrease (as measured by nFA) is truly linear or if the decrease becomes more accelerated over time, with increasing age, or with specific vascular risk factors. Second, because previous studies have shown that blood pressure reduction is associated with decreased WMH growth in community-based populations,\(^13\) the effect of such treatments on global and region-specific nFA values may warrant further study. Third, it will be important to define the precise relationship of changes in these white matter integrity measures to changes in cognition. Finally, as the authors point out, one hypothesis to explain the improvement seen in the FLAIR signal of stagnant lesions could be related to resolving inflammation. To address this question, the authors’ methodologies could potentially be used to study a cohort of patients with inflammation associated WMH, such as patients with multiple sclerosis or with cerebral amyloid angiopathy–related inflammation.\(^21\)

Although the character in Art fails to sway his friend that all that is white is not the same, the investigators in this study convincingly demonstrate that there is considerable nuance in things that appear white and that these nuances may be critical in the design of future intervention strategies to prevent cerebral white matter damage and cognitive impairment in the elderly.

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**Disclosures**

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