White Matter Hyperintensity Penumbra

Pauline Maillard, PhD; Evan Fletcher, PhD; Danielle Harvey, PhD; Owen Carmichael, PhD; Bruce Reed, PhD; Dan Mungas, PhD; Charles DeCarli, MD

Background and Purpose—White matter hyperintensities (WMHs) are associated with progressive age-related cognitive decline and cardiovascular risk factors, but their biological relevance as indicators of generalized white matter injury is unclear. Diffusion tensor imaging provides more sensitive indications of subtle white matter disruption and can therefore clarify whether WMHs represent foci of generalized white matter damage that extends over a broader neighborhood.

Methods—Two hundred eight participants from the University of California, Davis Alzheimer’s Disease Center received a comprehensive clinical evaluation and brain MRI including fluid-attenuated inversion recovery and diffusion tensor imaging sequences. Voxelwise maps of WMHs were produced from fluid-attenuated inversion recovery using a standardized WMH detection protocol. Fractional anisotropy maps were calculated from diffusion tensor imaging. All WMH and fractional anisotropy maps were coregistered to a standardized space. For each normal-appearing white matter voxel in each subject fluid-attenuated inversion recovery scan, a neighborhood white matter injury score was calculated that increased with increasing number and proximity of WMH in the vicinity of the normal-appearing white matter voxel. Fractional anisotropy was related to neighborhood white matter injury using a nonlinear mixed effect model controlling for relevant confounding factors.

Results—Fractional anisotropy was found to decrease as neighborhood white matter injury increased ($\beta = -0.0017/\%$, $P < 0.0001$) with an accelerated rate ($P < 0.0001$) for neighborhood white matter injury $>0.4$. An increase of 1% in neighborhood white matter injury score was associated with a decrease in mean fractional anisotropy of 0.012 ($P < 0.001$).

Conclusions—WMH may represent foci of more widespread and subtle white matter changes rather than distinct, sharply delineated anatomic abnormalities. We use the term white matter hyperintensities penumbra to explain this phenomenon. (Stroke. 2011;42:1917-1922.)

Key Words: aging ■ Alzheimer disease ■ cerebrovascular disease ■ diffusion tensor imaging ■ magnetic resonance imaging ■ white matter hyperintensity

White matter hyperintensities (WMHs) are a common finding in brain MRI images of older individuals, increasing with age and vascular risk factors.1,2 Although resulting from multiple etiologies, increased WMHs are associated with cognitive impairment3–6 and future risk for incident stroke and death7 emphasizing the importance of understanding the role of WMH in health and cognition. Pathological studies find no relationship between WMH and Alzheimer disease (AD) pathology8 but find expression of ischemic changes.9 Furthermore, recent studies suggest that WMHs are common to white matter watershed areas10 supporting the notion that at least some of these lesions are vascular in origin, yet the exact evolution of WMH remains unclear. For example, Schmidt et al11 identified 2 categories of WMH lesions: punctuate lesions that were considered relatively benign and confluent or early confluent lesions, which progressed rapidly in size over time. They postulated that these more confluent areas represented white matter regions where the disease process is progressively affecting an area at risk in a fashion similar to the ischemic penumbra of acute infarction (we use the most general definition of the term “penumbra”: a surrounding region in which a property exists to a lesser degree. Unlike the more specific use of the term in vascular neurology, the general use does not ascribe any specific biological mechanism such as ischemia to the phenomenon).

Newer studies using diffusion tensor imaging and measures of fractional anisotropy (FA) support the notion of injury to white matter integrity beyond the area of WMH to include normal-appearing white matter.12 As such, FA analysis may reveal subtle changes in areas surrounding WMH. We hypothesize that WMHs constitute evidence of a core white matter injury surrounded by a region reflecting more subtle white matter injury, which we described as a penum-
Informed consent. Institutional Review Boards at all participating institutions approved to current consensus criteria. As part of the clinical evaluation, the Davis Imaging Research Center on a 1.5-T GE Signa Horizon LX All brain imaging was performed at the University of California, Davis. All participants received a comprehensive clinical evaluation and neuropsychological testing. Subjects included 45 patients with AD, 67 patients with mild cognitive impairment, and 96 with cognitively normal individuals.

Materials and Methods

Sample

Subjects included 45 patients with AD, 67 patients with mild cognitive impairment, and 96 with cognitively normal individuals. The AD group consisted of 88.9% patients with probable AD, 8.9% patients with possible AD, and 2.2% patients with AD and sufficient cerebrovascular disease for the diagnosis of mixed dementia. This was defined as ≥2 strokes, at least 1 of which is outside the cerebellum on MRI, or else a single stroke with clearly documented temporal relationship to the onset or aggravation of cognitive impairment. No subjects except those with mixed dementia had a clinical history of stroke. The diagnosis of AD was made according to the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria. Mild cognitive impairment was diagnosed according to current consensus criteria. As part of the clinical evaluation, the presence or absence of stroke, diabetes, hyperlipidemia, transient ischemic attack, hypertension, and coronary artery disease was systematically assessed to create a composite score for vascular risks, which was the sum of the factors present, ranging from 0 to 6, and reported as a percentage.

Subjects were recruited from the Alzheimer’s Disease Center at the University of California, Davis. All participants received a comprehensive clinical evaluation and neuropsychological testing with a standardized test battery. In addition, all subjects received a standardized MRI scan of the brain at the baseline evaluation. The Institutional Review Boards at all participating institutions approved this study, and subjects or their legal representatives gave written informed consent.

Image Acquisition and Processing

All brain imaging was performed at the University of California, Davis Imaging Research Center on a 1.5-T GE Sigma Horizon LX Echospeed system. Three sequences were used: a 3-dimensional T1-weighted coronal spoiled gradient-recalled echo acquisition, a fluid-attenuated inversion recovery sequence, and a diffusion tensor imaging sequence. Diffusion tensor imaging was performed according to previously reported methods.

The segmentation of WMH was determined from fluid-attenuated inversion recovery images according to an in-house procedure that has been previously described. For each subject, we calculated the total volume of WMHs and normalized this measurement for head size by dividing by total cranial volume. Because the distribution of total WMH volume across the population was skewed, it was log-transformed to normalize the distribution. FA maps were calculated from diffusion tensor imaging. Using a previously described image registration method, WMH and FA maps were linearly aligned to the corresponding T1-weighted scan, which was then linearly aligned and nonlinearly deformed to a minimal deformation template (MDT) with a 0.98×1.5×0.98-mm³ voxel size. These alignments allowed the transfer of all FA and WMH maps to the space of the MDT. The average of the 208 WMH maps across all participants in this study is given in the online Supplement section, Figure II (http://stroke.ahajournals.org). Maps of gray matter and white matter in the space of the MDT have been generated using previously described tissue segmentation methods.

We created an average young adult FA map as previously described for comparison with the individuals of the present study. This map was made by averaging 15 healthy young adult FA images (mean age, 24.1±3.1 years; 60.0% male).

Calculation of Neighborhood White Matter Injury Score and Relation to FA

Our analytic approach was designed to estimate the weighted distance of each normal-appearing white matter voxel to WMH voxels across the entire image to examine how regional WMHs affect FA in normal-appearing white matter. To accomplish this task, we first needed to identify the distance of each white matter voxel to all other white matter voxels in the common stereotaxic space of the MDT. Then, for each subject, we identified each normal-appearing white matter voxel and calculated the distance of these voxels to every WMH within that individual’s image. From each normal-appearing white matter voxel in the image, we then calculated the NWI value by adding up the number of WMHs in the image divided by the distance from the normal-appearing white matter voxel of interest. As a consequence, normal-appearing white matter voxels in an area distant from WMH will have very low NWI scores, whereas normal-appearing white matter voxels near WMH will have higher NWI scores. Moreover, the more WMH near to the normal-appearing white matter voxel of interest, the higher the NWI score. This analytic method, therefore, measures the full effect of WMH in the vicinity of each normal-appearing white matter voxel for each subject.
This method was implemented as follows: we first calculated, for each MDT white matter voxel i, the number of white matter voxels located at distance j (mij), for j ranging between 1 mm and its maximum, 214 mm. Then, for each subject and MDT white matter voxel i, we used that individual’s WMH map in MDT space to calculate the number of voxels located at distance j, which were WMH (nj) for each normal-appearing white matter voxel. The ratio of mij to nj can be interpreted as the probability (pij) that any randomly selected voxel that is at distance j from i is WMH. The NWI for a voxel i adds together these WMH injury probabilities over a range of distances j to encapsulate the notion that an increased amount of WMH in the vicinity of i may be associated with an increased degree of white matter injury at i. In addition, the NWI downweights the influence that WMHs at larger distances from i have on this sum to encapsulate the notion that the more proximal a WMH is to voxel i, the more severe its impact on the white matter integrity at i. The influence of a WMH on white matter integrity falls off by the square of its distance to voxel i; thus, the NWI score for voxel i is given by the weighted sum (σ pij/j^2), normalized by (σ 1/j^2) (Figure 1).

For each individual, the NWI score was calculated at each white matter voxel in the MDT space, resulting in an NWI score map across the brain. The NWI score was then discretized to 1 of 10 integer values by breaking up the range of values from 0 to 1 into 10 intervals that were 0.1 U in width; each subject white matter voxel in MDT space was then labeled according to which of these intervals its NWI score fell into. We then calculated, for each subject and for each NWI score interval using an individual’s FA map, the mean FA value among WMH voxels in that interval. Mean FAs within NWI score intervals that included <10 voxels were omitted from the analysis. (Changing this threshold from 10 to 5 voxels did not significantly change the findings.)

Statistical Analysis
The primary goals of the statistical analysis were to determine the strength and nature of the association between mean FA and NWI score interval within each individual and to characterize commonalities and differences between individuals in the characteristics of this relationship. A secondary goal was to assess whether a variety of relevant factors served to systematically modify how mean FA relates to NWI score interval. Nonlinear mixed-effects regression was used to achieve these goals. Because the mean FA appeared to be quadratically related to NWI score interval on visual inspection (Figure 2, upper part), mean FA was modeled as a quadratic function of NWI score interval within each individual; that is, the within-individual model of mean FA included linear and quadratic terms for the fixed effect of NWI score interval. In addition, total WMH volume was added to the model as a fixed effect impacting mean FA as well as the linear and quadratic relationship between mean FA and NWI score interval. Interindividual differences in the mean FA–NWI score interval relationship were modeled using random effects for the intercept as well as linear and quadratic NWI score interval terms. We tested whether the random intercept and slopes were necessary, omitting them 1 by 1 from the original model and using the likelihood-ratio test to contrast each refit model with the reference. Each refit model was found significantly different from the reference model (P<0.001) justifying the inclusion of all random effects.

We then used a stepwise model-building approach to adjust this model for potential confounders, including gender, age, clinical diagnosis (cognitionally normal, mild cognitive impairment, or AD), Apolipoprotein E (APOE) genotype, number of years of education, and vascular risk, 1 at a time. Because APOE is a common stratification variable in AD studies, we also adjusted the reference model by the interaction between APOE and clinical diagnosis. In addition, because cognitive diagnosis may interact with overall WMH load, we conducted in a separate analysis the reference model across cognitively normal individuals only.

Continuous variables were mean centered in all analyses. Statistical analyses were performed using R Version 2.10.0 (R Development Core Team, Vienna, Austria).

Results
Demographics
Table 1 summarizes participant characteristics. The 3 clinical groups did not differ significantly in terms of age, cardiovascular risks, education level, or gender distribution but, predictably, the AD group included a higher proportion of APOE ε4-carriers relative to cognitively normal. Individuals with AD also exhibited higher total WMH volume compared with cognitively normal subjects.

Visualization of NWI Score and FA
Figure 3 provides an example of white matter alteration inside the core of a WMH and in its penumbra for 1 individual in this study. As expected, FA and fluid-attenuated inversion recovery images showed respectively lower and higher values inside the lesion (Figs 3A and 3C). Using the map of mean FA across a healthy young population sample as a reference (Figure 3B), we observed that FA was relatively reduced in this subject within the WMH as well as in the surrounding peripheral white matter (Figure 3D). The map of NWI score for this individual (Figure 3D) reflects this pattern of reduced white matter integrity in the WMH periphery. Note that NWI drops precipitously within 3 to 4 voxels of a WMH lesion as shown in Figure 3D.

Figure 4 illustrates the average of the 208 NWI score maps across all participants in this study. This map suggests that NWI score is relatively increased at systematic locations in the brain, especially in the periventricular zones where WMHs tend to accrue. Because of the rapid decline in NWI from surrounding WMH, this map closely parallels that of a map of average WMH for the group (see http://stroke.ahajournals.org).

Effect of NWI on FA
Mean FA was found to be 0.37 (Table 2). Each 10% of increasing NWI score was associated with a decrease in FA of...
An increase of 1% in WMH burden was significantly associated with decreasing mean FA of 0.012 ($P$=0.0001) and this decrease accelerated with increasing NWI score (Table 2). Figure 2 (upper part) shows the regression curves relating NWI score interval to mean FA in each subject. Both linear and quadratic decreases in FA due to NWI were found to be larger in individuals exhibiting higher overall WMH burden (Table 2).

### Overall WMH Load Effect

An increase of 1% in WMH burden was significantly associated with a decrease in mean FA of 0.012 ($P$=0.0001) and this rate accelerated with increasing WMH score interval (Table 2). To illustrate such interaction, we calculated WMH load quartiles (Quartile 1=[0.029; 0.179], Quartile 2=[0.179; 0.465], Quartile 3=[0.465; 1.105] and Quartile 4=[1.105; 6.981]) and computed mean FA related to the NWI score interval across subjects pooled according to their overall WMH loads broken into quartiles (Figure 2, lower part).

### Confounders

Cognitive diagnosis was not significant ($P$=0.33) indicating that mean FA, with respect to overall WMH load and NWI score interval, was independent of cognitive status. In the separate analysis conducted in cognitively normal individuals group ($N$=96), all effects indicating a significant inverse relationship between mean FA and NWI interval and overall WMH load (Table 2) remained significant.

None of the other potential confounders significantly modified the relationship between mean FA and NWI score interval (age: $P$=0.36, APOE: $P$=0.87, APOE by cognitive diagnosis: $P$=0.86, education: $P$=0.24, vascular risk: $P$=0.18, gender: $P$=0.41).

### Mean Diffusivity

An identical analysis was performed for mean diffusivity. These results are included in the online Supplement section and were essentially the inverse of the FA results. That is, as NWI went up, mean diffusivity increased significantly. Moreover, average mean diffusivity increased with the total extent of WMH burden (see http://stroke.ahajournals.org).

### Discussion

The present study aimed to better understand the role of WMH on local white matter architecture. The first finding of this study is that WMHs appear to be at the apex of the white matter alteration because FA measures of white matter integrity surrounding WMH decline in proximity to WMH. We use the term WMH penumbra to explain this phenomenon. The second result is that generalized white matter integrity is a function of the overall WMH load. The greater the total WMH load, the more generalized the white matter injury, including areas extremely distant from WMH. Importantly, both findings were found to be independent of cognitive diagnosis.

These results are significant for 2 reasons. First, the presence of a WMH penumbra strongly suggests that WMHs indicate a process that extends beyond the region of tissue pathology determined by selecting any particular fluid-attenuated inversion recovery intensity threshold to define WMH. This finding may have biological implications. For example, we have previously shown that periventricular WMHs occur in anatomic areas consistent with vascular watershed with peak WMH prevalence approximately 3 to 4 mm from the ventricular edge.3 Our current findings are surprisingly consistent in that decline in FA surrounding areas of high white matter injury probability was on the order of 1 to 2 voxels or approximately 3 mm (Figures 2 and 3D). In both instances, we see a gradient of effect surrounding potential vascular distributions, the previous report at a global level and the current findings more locally. However, additional work is needed to determine exactly what biological mechanisms may be causing microstructural damage to surround WMHs.

Second, our findings strongly suggest that extensive WMHs result in altered white matter integrity throughout the cerebral white matter, particularly when WMH burden is extensive. This second finding is important to interpreting any differences in FA measurements in the absence of adjusting for total WMH burden in studies of older individuals in whom WMHs are more common. Few prior studies...
have examined the relationship between FA and total WMH loads in the elderly.\(^1\) We further propose that WMHs constitute only “the tip of the iceberg” and are only a crude estimate of white matter injury and should not be dissociated from the somewhat more subtle white matter impairments in white matter integrity in the WMH penumbra.

To our knowledge, this is the first study that provides in vivo evidence of an association between generalized white matter injury in 1 location and WMH in another. This work supports a previous study suggesting that, after WMH voxels are removed from FA maps, WMH volume is associated with regional loss of white matter integrity in regions prone to WMHs.\(^1\) Our results are also consistent with a recent postmortem study that found decreased microvascular density using alkaline phosphatase staining in subjects with leukoaraiosis as compared with subjects without leukoaraiosis, both within white matter lesions and the healthy appearing white matter outside the lesions.\(^2\) The weak associations between WMH and cognitive performances may be explained, as previously suggested,\(^2\) by an inappropriate dichotomization of white matter into WMH and normal-appearing WM. Our results indicate a method whereby we can better characterize the full impact of these more extensive losses of white matter integrity. Our results also support those of a previous study that reported negative and positive correlations between fluid-attenuated inversion recovery within WMH and FA and mean diffusivity, respectively.\(^2\) Our results extend their finding to all white matter, even white matter that is not immediately adjacent to WMH.

Table 2. Summary of the Nonlinear Mixed-Effects Model of Mean Fractional Anisotropy With NWI, NWI×NWI, and the WMH Load as Main Fixed Factors, Including NWI by WMH Load and NWI×NWI by WMH Load Interactions*  

|                | All (n=208) |   | CN (n=96) |   |
|----------------|-------------|------------------|------------------|
| Intercept (mean FA) | 0.370 <0.001 | 0.372 <0.001 |
| NWI            | -0.168 <0.001 | -0.164 <0.001 |
| NWI×NWI        | -0.406 <0.001 | -0.394 <0.001 |
| WMH load       | -0.012 <0.001 | -0.013 <0.001 |
| NWI by WMH load| -0.039 <0.001 | -0.056 <0.001 |
| NWI×NWI by WMH load| -0.082 <0.001 | -0.105 <0.001 |

WMH indicates white matter hyperintensity; FA, fractional anisotropy; NWI, neighborhood white matter injury; CN, cognitively normal.

*Entries show the regression coefficient for the listed fixed effect followed by the associated P value for an F test on the marginal sum of squares.
The key limitation of the study was that we assumed that the impact of a WMH on a normal white matter location depended solely on the straight-line distance between the 2 measures without taking into account the architecture of the underlying network of axonal tracts. In fact, it may be more biologically plausible to assume that WMH at 1 location on a white matter tract more strongly influences white matter integrity along the rest of the same tract than in others. Future work should explore the use of diffusion tensor imaging tractography to model WMH penumbra effects more realistically in this fashion.

Conclusions

This study provides evidence of the existence of a penumbra of white matter injury in the so-called normal white matter surrounding WMH. White matter integrity locally is associated with the overall WMH load globally; and it is more compromised at locations that are closer to WMH. Aging-associated mechanisms of white matter degeneration are complex and this work suggests new considerations to better assess the broader spectrum of white matter injury.

Sources of Funding

The study was supported by National Institutes of Health grants K01 AG030514, R01 AG010220, R01 AG 031563, R01 AG021028, and P30 AG010129.

Disclosures

None.

References

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Stroke. 2011;42:1917-1922; originally published online June 2, 2011; doi: 10.1161/STROKEAHA.110.609768

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/7/1917

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Supplemental Methods

Sample

Subjects included 44 patients with Alzheimer Disease (AD), 66 patients with mild cognitive impairment (MCI), and 96 with cognitively normal (CN) individuals. The AD group consisted of 88.6% patients with probable AD, 9.1% patients with possible AD, and 2.3% patients with AD and sufficient cerebrovascular disease for the diagnosis of mixed dementia. Mean (SD) age was 76.4 (9.6), 73.4 (7.2) and 74.3 (7.5) for AD, MCI and CN groups respectively.

Calculation of neighbourhood white matter injury score and relation to Mean Diffusivity

For each individual, the NWI score was calculated at each WM voxel in the MDT space, resulting in an NWI score map across the brain. The NWI score was then discretized to one of ten integer values by breaking up the range of values from 0 to 1 into ten intervals that were .1 units in width; each subject WM voxel in MDT space was then labelled according to which of these intervals its NWI score fell into. We then calculated, for each subject and for each NWI score interval using individual’s MD map, the mean MD value amongst WM voxels in that interval. Mean MD within NWI score intervals that included fewer than 10 voxels were omitted from the analysis.

Statistical analysis

Nonlinear mixed-effects regression was used to achieve these goals. Because the mean MD appeared to be cubically related to NWI score interval on visual inspection
(Figure S3), mean MD was modelled as a cubic function of NWI score interval within each individual using a nonlinear mixed-effects regression; that is, the within-individual model of mean MD included linear, quadratic and cubic terms for the fixed effect of NWI score interval. In addition, total WMH volume was added to the model as a fixed effect impacting mean MD as well as the linear, quadratic and cubic relationships between mean MD and NWI score interval. Inter-individual differences in the mean MD – NWI score interval relationship were modelled using random effects for the intercept as well as linear, quadratic and cubic NWI score interval terms.

Continuous variables were mean centered in all analyses. Statistical analyses were performed using R version 2.10.0 (R Development Core Team, 2009, Vienna, Austria).
### Supplemental Tables

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<td>NWI by WMH load</td>
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S1: Summary of the nonlinear mixed effects model of Mean Diffusivity (MD) average with NWI, NWI x NWI, NWI x NWI x NWI and the WMH load as main fixed factors, including NWI by WMH load. Entries show the regression coefficient for the listed fixed effect followed by the associated p value for an F test on the marginal sum of squares.

WMH: White Matter Hyperintensities

NWI: Neighbourhood White matter Injury
Supplemental Figures

S2: Axial slices of the average (across subjects) white matter hyperintensities (WMH) maps in the minimal deformation template space. Mean WMH are given by the colour scale. WMH maps are superimposed on the average T1-weighted images of the sample.
S3: Upper part: regression curves of Mean Diffusivity (MD) average as a cubic function of the neighbourhood white matter injury (NWI) score across the 206 subjects. Lower part: Mean MD according to NWI scores and overall WMH load quartiles