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# Anatomical Mapping of White Matter Hyperintensities (WMH)

## Exploring the Relationships Between Periventricular WMH, Deep WMH, and Total WMH Burden

Charles DeCarli, MD; Evan Fletcher, PhD; Vincent Ramey; Danielle Harvey, PhD; William J. Jagust, MD

**Background and Purpose**—MRI segmentation and mapping techniques were used to assess evidence in support of categorical distinctions between periventricular white matter hyperintensities (PVWMH) and deep WMH (DWMH). Qualitative MRI studies generally identify 2 categories of WMH on the basis of anatomical localization. Separate pathophysiologies and behavioral consequences are often attributed to these 2 classes of WMH. However, evidence to support these empirical distinctions has not been rigorously sought.

**Methods**—MRI analysis of 55 subjects included quantification of WMH volume, mapping onto a common anatomical image, and spatial localization of each WMH voxel. WMH locations were then divided into PVWMH and DWMH on the basis of distance from the lateral ventricles and correlations, with total WMH volume determined. Periventricular distance histograms of WMH voxels were also calculated.

**Results**—PVWMH and DWMH were highly correlated with total WMH ( $R^2 > 0.95$ ) and with each other ( $R^2 > 0.87$ ). Mapping of all WMH revealed smooth expansion from around central cerebrospinal fluid spaces into more distal cerebral white matter with increasing WMH volume.

**Conclusion**—PVWMH, DWMH, and total WMH are highly correlated with each other. Moreover, spatial analysis failed to identify distinct subpopulations for PVWMH and DWMH. These results suggest that categorical distinctions between PVWMH and DWMH may be arbitrary, and conclusions regarding individual relationships between causal factors or behavior for PVWMH and DWMH may more accurately reflect total WMH volume relationships. (*Stroke*. 2005;36:50-55.)

**Key Words:** cerebrovascular disorders ■ magnetic resonance imaging ■ white matter

White matter hyperintensities (WMH) are commonly seen on T2-weighted MRI and are often divided into 2 categories: periventricular WMH (PVWMH), which abut the cerebral ventricles, and deep WMH (DWMH), which are patchy areas of WMH in subcortical white matter distinct from the periventricular area.<sup>1-8</sup> Qualitative MRI studies evaluating the impact of vascular risk factors on WMH routinely distinguish PVWMH from DWMH.<sup>6,9-14</sup> Results from these studies generally show age and vascular risk factors as the strongest correlate of PVWMH, whereas associations between vascular risk factors and DWMH are much weaker. Similarly, studies examining the relationship between PVWMH, DWMH, and cognitive performance among nondemented elderly<sup>15</sup> generally find strong correlations between PVWMH and cognitive measures<sup>15,16</sup> but not DWMH. MRI pathological correlations of WMH also suggest differences between PVWMH and DWMH.<sup>9,17-26</sup> However, within both types of WMH lesions, there is vascular fibrosis

and lipohyalinosis,<sup>9,22,23,25-27</sup> supporting a common ischemic vascular pathological mechanism for WMH among older individuals.<sup>17,24,25</sup> Therefore, whereas qualitative MRI studies generally support distinctions between PVWMH and DWMH, pathological studies suggest that both types of WMH share the same ischemic etiology supporting pathological linkage. However, most previous MRI work has used qualitative single-slice assessments that may not fully appreciate the complex 3D anatomy of WMH. Thus, existing MRI data cannot unequivocally support distinctions between PVWMH and DWMH. This study sought to confirm these anatomical distinctions using new image segmentation and mapping techniques.

### Methods

#### Subjects

Subjects for this study consisted of the first 55 consecutive individuals recruited through the University of California at Davis (UCD)

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**Subject Demographics, WMH, and Brain Volumes**

Variable	No Cognitive Impairment	CIND	Dementia
No.	17	22	15
Gender (male/female)	6/11	12/10	7/8
Age, y	72.7±11.9	73.5±8.3	78.5±6.0
MMSE	29.3±0.8	26.5±3.5	22.2±5.9
WMH volume*	0.79±0.85	0.76±0.93	1.57±1.59
Brain volume*	81.0±4.8	78.7±3.5	77.1±3.9

\*Expressed as percentage of total cranial volume. MMSE indicates mini mental state examination.

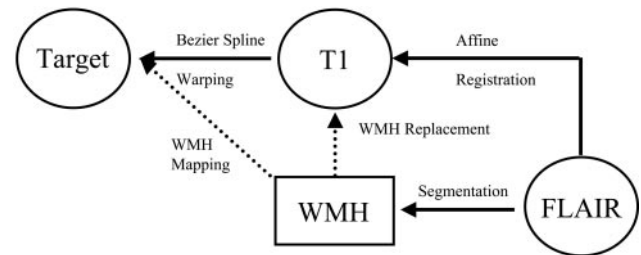
Alzheimer's Disease Center for whom research MRI was available for analysis. As expected, these individuals had variable cognitive abilities ranging from normal to cognitive impairment not demented (CIND) to dementia as defined according to standard diagnostic criteria.<sup>28,29</sup> Etiologies of cognitive impairment included Alzheimer's disease (AD) and cerebrovascular disease (CVD), including symptomatic stroke, although individuals with cortical infarctions were excluded. Subjects were recruited for participation through advertisements, community screening, and physician referrals. Subject demographics according to cognitive syndrome are summarized in the table. Informed consent was obtained for each patient at the time of participation in the study according to UCD institutional review board guidelines.

**MRI Sequences**

All brain imaging was obtained at the UCD MRI research center on a 1.5T GE Signa Horizon LX EchoSpeed system. Two sequences were used: a T1-weighted coronal 3D spoiled gradient recalled echo acquisition and a fluid-attenuated inversion recovery (FLAIR) sequence designed to enhance WMH segmentation.<sup>30</sup>

**Image Analysis**

An overview of image analysis is summarized in Figure 1. In brief, image segmentation using previously described algorithms<sup>31,32</sup> was applied to the FLAIR sequences to segment WMH (Figure 2). After affine coregistration of the FLAIR image to the high-resolution T1 image, WMH voxels were used to correct intensity changes in the T1 image to reduce any adverse impact of the WMH voxel values on the accuracy of the nonlinear warping algorithm. The details and



**Figure 1.** Schema for WMH segmentation and nonlinear transformation for mapping. See text for details.

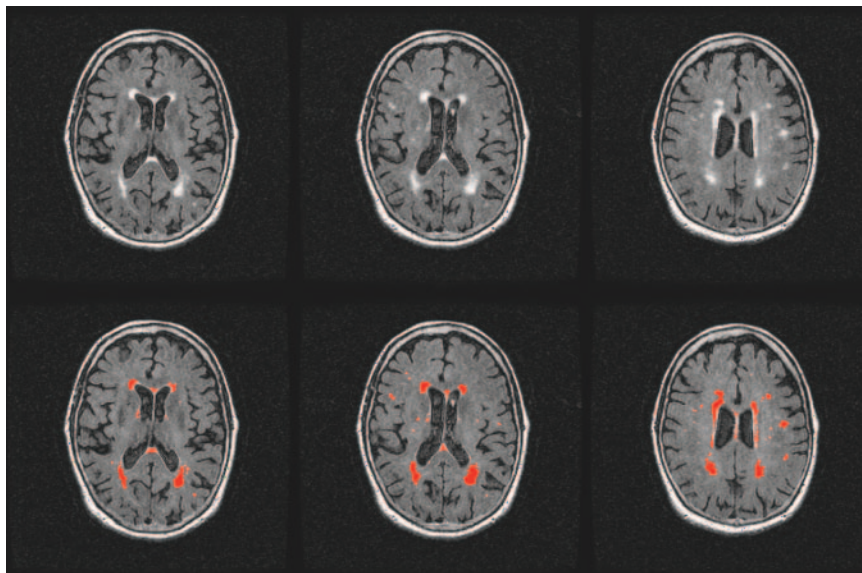
rationale for these processes are included in an appendix available online only at <http://www.strokeaha.org>.

**Data Analysis**

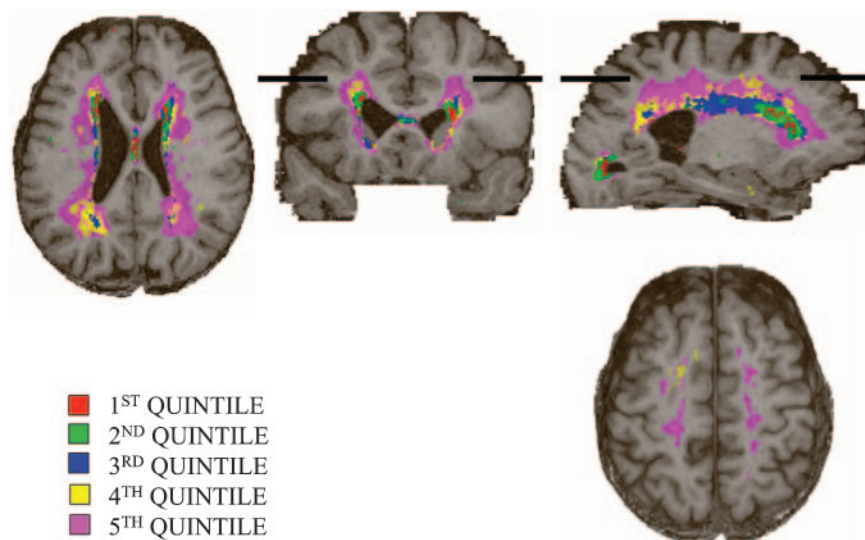
Nonlinear warping enables precise matching of anatomical regions across subjects (see online appendix). We used this characteristic of the method to determine the exact distance between each WMH voxel and the ventricular endymal surface for all subjects. To test the hypothesis of the PVWMH versus DWMH distinction, we measured distributions of WMH voxels in reference to the endymal surface of the target ventricular system in 2 ways. We first created histograms of the average distance from the ventricular surface for 5 quintiles of WMH burden. We hypothesized that if a true distinction in WMH location (ie, PVWMH versus DWMH) were present, we would see 2 peaks in the histograms related to the separate WMH categories. Second, we created a standardized division of WMH location into PVWMH and DWMH on the basis of 1-cm distance from the ventricular system. Volumes for PVWMH and DWMH were then calculated for each individual subject. Linear regression analysis was used to examine PVWMH and DWMH volumes in relation to total WMH volume and each other.

**Results****Subjects**

There were no significant differences in age across the groups, although subjects with dementia tended to be somewhat older (Table). Among the dementia subjects, 9 were diagnosed as clinically probable AD, and 6 were diagnosed as mixed dementia with AD and CVD combined. A total of 8 subjects had clinical stroke that presented as a lacunar



**Figure 2.** Example of FLAIR segmentation method.



**Figure 3.** Mean voxel distributions according to quintile of WMH burden. Black hatch marks indicate level of axial image shown below and illustrate the limitations of 2D viewing for determination of WMH location.

syndrome, predominantly with hemiparesis. Of the 8 with clinical stroke, 6 were demented and 2 had CIND. No subjects had cerebral hemorrhage.

### WMH Volumes

WMH volumes were calculated for all subjects and ranged from 1.1 to 63 mL and divided into quintiles with ranges consisting of first, 1.1 to 2.3 mL; second, 2.6 to 4.6 mL; third, 5.1 to 9.0 mL; fourth, 9.7 to 16.0 mL; and fifth, 18.0 to 63 mL. There were no significant differences in mean WMH volumes in association with degree of cognitive impairment (Table), although subjects with dementia had nearly twice the volume of WMH.

### WMH Distributions

Mapping of subjects by quintile of total WMH volume (Figure 3) revealed a continuous gradient of mapped WMH voxels extending from around the cerebrospinal fluid (CSF) ventricular system in direct relation to calculated WMH volume. Evidence for the potential misclassification of DWMH on the basis of 2D visualization is also illustrated (Figure 3). When viewed axially, as is common in studies of WMH,<sup>33,34</sup> DWMH appear present. However, the sagittal and coronal orientations show that these WMH are actually contiguous with the ventricular lining.

Distance histograms of WMH voxels are shown in Figure 4. There is no clear sign of a bimodal distribution. Instead, the peak of the WMH distribution widens continuously from the lowest WMH quintile, where the median distance is  $\approx 3.5$  mm, to highest quintile, where the median distance is  $\approx 6.0$  mm. One exception to this general observation is at the lowest quintile, where a small second peak occurs at  $\approx 30$  mm from the ventricular surface. Examination of the images in the lowest quartile of WMH revealed the presence of multiple punctate WMH scattered within the centrum semiovale.

In the second analysis, WMH were divided into PVWMH and DWMH on the basis of a 1-cm distance from the ventricular surface. The relationship between PVWMH, DWMH, and total WMH burden is graphically illustrated in Figure 5. PVWMH and DWMH volumes were closely associated with WMH burden ( $R^2=0.99$  and  $0.92$ , respectively). PVWMH and DWMH volumes also were signifi-

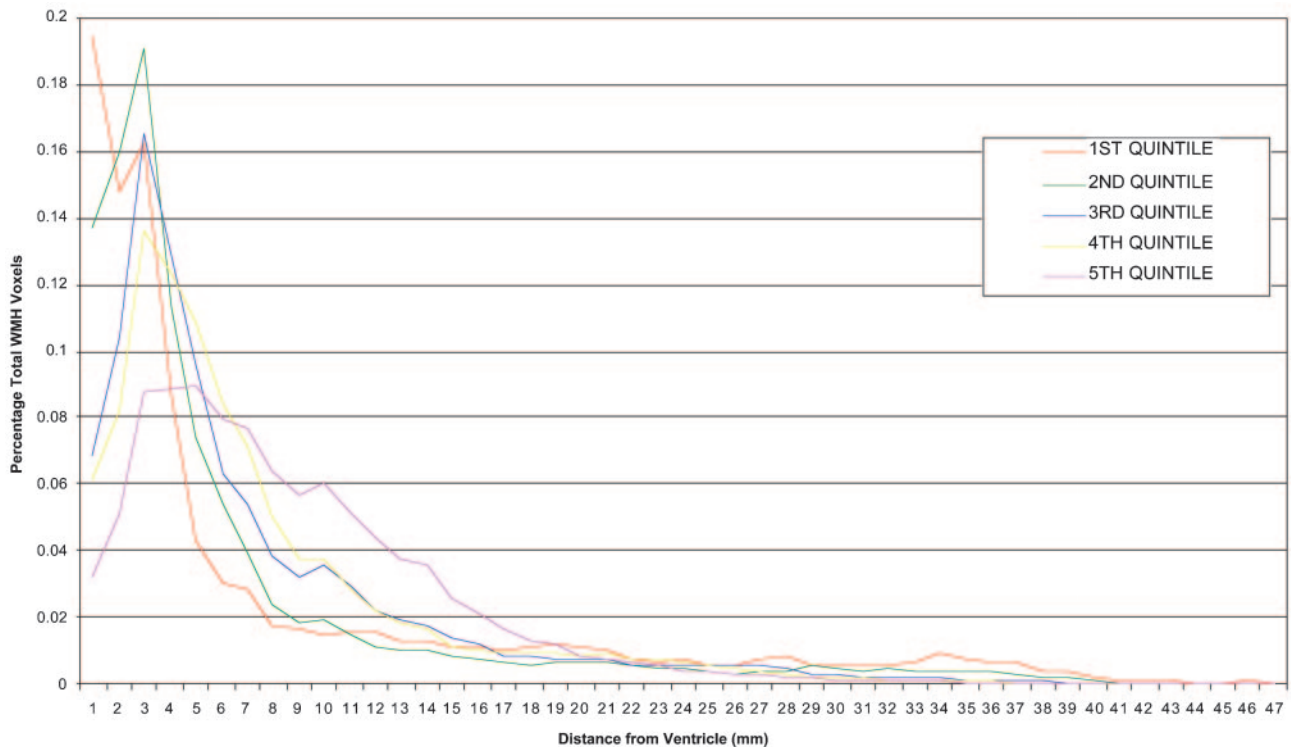
cantly correlated ( $R^2=0.87$ ). The slope of PVWMH to total WMH burden is  $\approx 2.5\times$  that of the slope between DWMH and total WMH burden, suggesting a preferential increase in PVWMH with increasing total WMH burden.

### Discussion

Use of image segmentation, 3D anatomical mapping of WMH voxels, and 2 separate analytical methods failed to find distinctions between PVWMH and DWMH. Not only did analyses of distance histograms fail to identify 2 separate WMH voxel populations, but application of a standard categorical definition for PVWMH versus DWMH across all subjects found high correlations with total WMH burden as well as with each other. These results suggest that categorical distinctions between PVWMH and DWMH are likely to be arbitrary, and conclusions regarding individual relationships between causal factors or behavior for PVWMH and DWMH may more accurately reflect total WMH volume relationships. However, our data cannot speak to possible regional differences in pathological processes for PVWMH and DWMH but do show that both phenomena are highly correlated with each other, suggesting a common underlying mechanism.

Our results appear different from visual inspection (Figure 2) as well as published examples of WMH.<sup>8,33</sup> One obvious explanation for this discrepancy is our use of 3D mapping techniques that may avoid some of the limitations of 2D qualitative MRI studies. For example, we show that WMH typical of DWMH, when viewed axially, are in fact contiguous with ventricular WMH (Figure 3). This finding is not specific to our method because a recently published Statistical Parametric Mapping study found similar results,<sup>35</sup> although it did not specifically examine the question of PVWMH versus DWMH. A second explanation for differing results also may derive from our use of consistent measures and anatomical definition of PVWMH versus DWMH. For example, in the Rotterdam Scan Study, DWMH are measured according to width and number as opposed to categorical definitions for PVWMH,<sup>8</sup> making direct comparisons between the 2 types of WMH difficult. Different measures for DWMH versus PVWMH may also explain differences in





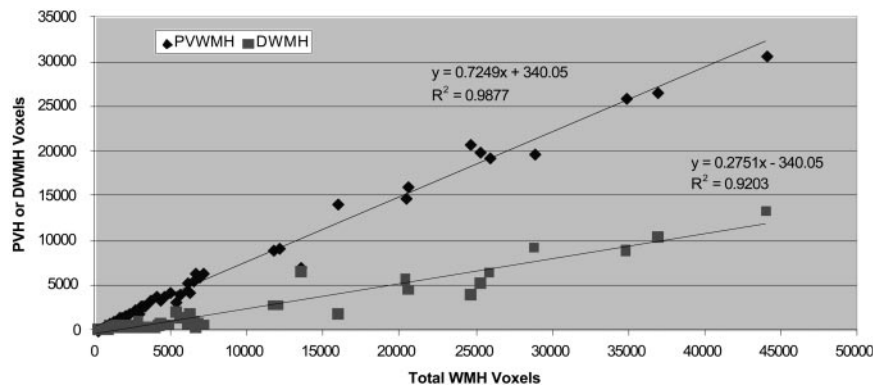
**Figure 4.** Distance histogram distributions according to quintile of WMH burden.

associations between causal factors, behavior, and DWMH found with qualitative studies.<sup>15,16</sup> However, our conclusions are not meant to suggest that islands of abnormal WMH signal located in the centrum semiovale do not exist. Quite the contrary; we believe that our data support the notion proposed by Schmidt et al<sup>36</sup> that WMH burden increases through the confluence of PVWMH with punctate WMH located in the centrum semiovale, although our experiment was not designed to address this particular question. However, our histogram data do support this hypothesis by showing a second peak at the lowest quintile of WMH volume, indicating more frequent DWMH initially that may then converge with PVWH as the total WMH increases. We further suggest that the strong correlations between causal factors and behavior found with PVWMH in qualitative studies likely reflect the steeper slope of change of PVWMH with total WMH burden, as seen with our quantitative data analysis (ie, the steeper slope suggests increased sensitivity to detect differences across individuals).

Our results are also consistent with current concepts of WMH pathology. Although some controversy remains,<sup>37</sup> there is general consensus for a single vascular white matter watershed area extending between 3 and 13 mm from the ventricular surface,<sup>37–40</sup> remarkably similar to the distances described by our quantitative MRI analysis (Figure 4). However, some neuropathological evidence distinguishing different types of WMH lesions does remain.<sup>25</sup> For example, subependymal gliosis, irregularity of the ependymal lining, adjacent myelin pallor,<sup>22,23,25,41,42</sup> or a normal fasciculus subcallosus<sup>22</sup> are commonly found in postmortem samples when WMH are limited to ventricular capping or a smooth halo about the ventricles (eg, similar to WMH quintiles 1

through 3; Figure 3). Conversely, vascular hyalinization, ischemic white matter injury, and microscopic infarction are consistently found when the periventricular changes become extensive.<sup>17,24,25</sup> In these cases, DWMH sharing features of ischemic pathology commonly co-occur with PVWMH,<sup>25</sup> suggesting a pathophysiology common to both.<sup>17,24</sup> Although differences in pathological features argue strongly for separate categories of WMH, we believe these categories are different from designations of PVWMH or DWMH used for qualitative MRI studies. That is, minor degrees of WMH (rims and caps<sup>1</sup>) are most consistent with periventricular edema or disturbed CSF transport<sup>25,41,42</sup> and most likely accompany normal aging.<sup>32</sup> Conversely, more extensive WMH likely have a vascular etiology independent of designations such as PVWMH or DWMH.<sup>17,24,25</sup> Quantitative MRI studies support this distinction by showing strong associations between vascular risk factors and vascular disease when WMH volumes are extensive,<sup>32,43</sup> further supporting the notion that it is the overall extent and not categorical distinctions that best represent the underlying pathology of the WMH.

Because of a number of limiting factors, these results should be interpreted cautiously. First, our data are based on segmented WMH values and mathematical interpolation methods, raising the possibility that measurement error might reduce the sensitivity to identify a second population of WMH voxels. That is, our segmentation method favors selecting voxels of most extreme signal change, and our interpolation method induced a small amount of image smoothing. However, we do not believe that these errors were substantial because our segmentation of WMH is based strictly on voxel intensity parameters<sup>31,43</sup> and, therefore, would tend to underestimate the continuity of these changes



**Figure 5.** Relationship between PVWMH, DWMH, and total WMH burden.

by selecting only voxels above a specified threshold, favoring separate populations of WMH voxels. Minor degrees of image smoothing from image interpolation during warping are similarly unlikely to lead to substantial error in detection of separate voxel populations because the distinctions between PVWMH and DWMH are defined in more macroscopic terms.<sup>15,34</sup> Subject selection may be a second weakness of the study for 2 reasons. First, our population included individuals referred to or recruited for our memory disorders clinic and, therefore, is not representative of the general population. However, the patterns of WMH seen with the 55 subjects studied do not differ from other studies reporting various degrees of WMH severity.<sup>33,34</sup> Secondly, our sample included individuals with a wide range of cognitive abilities and concurrent CVD, although individuals with cortical infarction were excluded from the analysis. Although it has been suggested that individuals with cognitive impairment are more likely to have larger PVWMH compared with DWMH,<sup>44</sup> we would argue that this finding more closely reflects total WMH burden, as seen with other studies.<sup>45,46</sup> Therefore, although this is a sample of convenience that included individuals with differing degrees of cognitive impairment, the type and pattern of WMH seen were typical of those noted by population studies and would not be expected to alter the results found. However, our conclusions may not be directly applicable to other diseases such as late-life depression, in which frontal DWMH are significantly more common,<sup>47,48</sup> an area worthy of further investigation using these newer methods.

In conclusion, we believe the methods developed here conclusively show that WMH extend smoothly from the ventricular wall as the overall burden increases, offering no clear evidence for distinguishing WMH subtypes. In fact, these data support the notion of a single vascular watershed area that extends from the CSF ventricular surface to the central white matter, consistent with currently proposed cerebral vascular anatomy.<sup>37,38</sup> These observations also support the notion of a common ischemic etiology among elderly individuals when WMH burden is extensive.

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