With advancing age comes inevitable decline in most biological systems. Perhaps among the most devastating is the targeted brain dysfunction that accompanies aging, and its negative impact on cognitive and intellectual abilities. Descriptively, cognitive aging across individuals is heterogeneous. Some experience a precipitous and universal decline in cognitive abilities, while others experience more subtle downward cognitive trajectories in certain cognitive domains, with preservation or even improvement in others. From a taxonomic perspective, when age-associated cognitive

Structural neuroimaging in Alzheimer’s disease: do white matter hyperintensities matter?

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The targeted brain dysfunction that accompanies aging can have a devastating effect on cognitive and intellectual abilities. A significant proportion of older adults experience precipitous cognitive decline that negatively impacts functional activities. Such individuals meet clinical diagnostic criteria for dementia, which is commonly attributed to Alzheimer’s disease (AD). Structural neuroimaging, including magnetic resonance imaging (MRI), has contributed significantly to our understanding of the morphological and pathology-related changes that may underlie normal and disease-associated cognitive change in aging. White matter hyperintensities (WMH), which are distributed patches of increased hyperintense signal on T2-weighted MRI, are among the most common structural neuroimaging findings in older adults. In recent years, WMH have emerged as robust radiological correlates of cognitive decline. Studies suggest that WMH distributed in anterior brain regions are related to decline in executive abilities that is typical of normal aging, whereas WMH distributed in more posterior brain regions are common in AD. Although epidemiological, observational, and pathological studies suggest that WMH may be ischemic in origin and caused by consistent or variable hypoperfusion, there is emerging evidence that they may also reflect vascular deposition of β-amyloid, particularly when they are distributed in posterior areas and are present in patients with AD. Findings from the literature highlight the potential contribution of small-vessel cerebrovascular disease to the pathogenesis of AD, and suggest a mechanistic interaction, but future longitudinal studies using multiple imaging modalities are required to fully understand the complex role of WMH in AD.

Keywords: Alzheimer’s disease; MRI; white matter hyperintensity; beta amyloid

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While associative epidemiological studies play an important role by identifying correlates of poor cognitive aging or AD, they tell us little about directional causality or brain mechanisms involved in pathogenesis. Over the past three decades, the field of biomedical engineering has infused the clinical neurosciences with powerful neuroimaging instruments equipped to study directly morphological and functional properties of the aging brain in vivo. Advances in the acquisition, visualization, and analysis of neuroimaging data continue to evolve rapidly, with ongoing development of hardware, software, and conceptual statistical approaches that have already made tremendous scientific contributions. Structural magnetic resonance imaging (MRI) in particular can be used to examine macrostructural changes—gross differences in tissue volume that reflect volume variability, parenchymal atrophy, or frank pathology (e.g., large-vessel infarct, tumor); or microstructural changes—fiber tract integrity and pathology that can be altered due to subtle changes in myelin-associated pathology. Several studies have highlighted the importance of gross structural or volumetric changes in cognitive aging and dementia (for example, see refs 7-11; see ref 12 for review). Small-vessel cerebrovascular disease, visualized as white matter hyperintensities (WMH), has emerged as a particularly strong correlate of cognitive aging (for review, see ref 13) and is the focus of our discussion here.

Characterization and quantification of white matter hyperintensities

White matter hyperintensities, sometimes referred to as leukoaraiosis or leukoencephalopathy, are areas of increased lucency visualized on T2-weighted images. They have enjoyed a rich, albeit capricious, history in clinical practice and in the aging literature, at points considered incidental with little clinical significance and at points considered a central source of cognitive, motoric, and emotional dysfunction. Initially, WMH were described as “unidentifiable bright objects,” confounding radiologists as either artifactual or adventitious companions of aging. Indeed, chronological age is the strongest correlate of WMH severity and most older adults have some degree of WMH burden. Figure 1 displays a typical example of distributed WMH and Figure 2 shows examples of two elderly individuals, one with mild WMH and
one with more severe WMH reconstructed in three dimensions. White matter hyperintensities usually appear in the white matter confluent to the lateral ventricles (i.e., “periventricular” WMH), often projecting deep into cortical white matter and grey matter nuclei (i.e., “deep” WMH), or as circumscribed punctate spheres in deep cortical tissue. Of note, punctate WMH often appear as isolated lesions on two-dimensional MRI axial slices, but with three-dimensional reconstruction it often becomes evident that they are contained within the same process stemming off the lateral ventricles.

Optimal characterization of the severity of WMH among older adults has been a matter of some debate. Some authors have argued that periventricular WMH are clinically less important than deep WMH. Others have stressed the importance of regional, or lobar, distribution of WMH. These characteristics are reflected in many visual rating scales, such as the Scheltens Scale,\(^\text{17}\) which are commonly used to evaluate the severity and distribution of WMH. Our laboratory has developed a quantitative approach for regional WMH severity analysis. Briefly, by considering the distribution of voxel intensities on individual fluid attenuated inverse recovery (FLAIR) images, we fit Gaussian curves to each cerebral hemisphere and derive the mean and standard deviation for each hemisphere. White matter hyperintensity seeds are defined as greater than or equal to 2.5 standard deviations above the mean. The left and right seeds are combined, and each seed is then passed into a mean intensity-based region-growing algorithm. The algorithm uses the seed voxel intensity as its starting mean and, applying a 10-point connectivity scheme (x-y plane, and 1 up in z and 1 down in z-plane) it searches for and labels voxels that fall within 5% of the seed mean. Neighboring voxels that fall within 5% are added to the image and a new mean is created. This process continues iteratively until all seeds have been included in the final WMH image. The summation of the number of voxels labeled as WMH multiplied by voxel dimensions yields the total WMH volume. By spatially normalizing an anatomical atlas\(^\text{18}\) to each image, we are able to derive WMH volumes in each of the major anatomical lobes, basal ganglia, and cerebellum. Figure 3 illustrates three orthogonal views of a FLAIR image with WMH labeled and regionally parcellated. Furthermore, through segmentation of the lateral ventricles (Figure 4), we are able to cal-

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**Figure 1.** Typical distribution of white matter hyperintensities on a single subject's axial T2-weighted FLAIR raw image (left) and labeled with an intensity threshold (right). FLAIR, fluid attenuated inverse recovery.

**Figure 2.** Three-dimensional reconstruction of white matter hyperintensities (WMH) superimposed on a T1-weighted high resolution anatomical image. Patient on the left has relatively mild distribution of periventricular WMH; patient on the right has more severe distribution with WMH extending into deep cortical areas.
C l i n i c a l r e s e a r c h

calculate the distance in three dimensions of each voxel from the ventricular wall. Thus, our quantitative processing approach can be used to derive total WMH volume, regional WMH volume, and periventricular vs deep regional WMH volumes.

Correlates of white matter hyperintensities

Despite the ubiquity of WMH among older adults, they are a uniquely radiological phenomenon. That is, when examining grossly the brain regions underlying WMH, there is no obvious pigmentation abnormality. Our current understanding of the nature, clinical importance, and cognitive consequences of WMH has come from a number of careful clinicopathological correlates and observational studies among clinical and epidemiological samples. A prevailing view is that WMH are a surrogate marker of small-vessel vascular disease resulting from ischemic damage due to chronic hypoperfusion. White matter hyperintensities tend to develop in regions that are considered “watershed” areas, which extend up to 13 mm beyond the ventricular walls. Indeed, most of the major risk factors for ischemia have been shown to be associated with the severity of WMH distribution. Further evidence for an ischemic origin comes from post-mortem pathological examination of tissue that appears as WMH during life. Areas most vulnerable to development of WMH receive blood supply primarily from ventriculofugal vessels, which originate from the subependymal arteries. These vessels have relatively few anastomoses and are particularly vulnerable to injury due to systemic hypoperfusion. Clinico-pathological correlate studies have shown that smooth periventricular WMH are associated with subependymal gliosis and disruption of the ependymal lining, whereas deep white matter punctate WMH or irregularly shaped periventricular WMH are associated with disruption in fibers secondary to ischemic/arteriosclerotic changes. In general, WMH are related to diminished pallor or rarefaction and gliosis and myelin or axonal loss.

By combining structural neuroimaging data with measures of cerebral blood flow, as measured by arterial spin labeling (ASL), we showed that areas appearing as WMH on FLAIR images had diminished blood flow relative to normal appearing white matter and grey matter. The finding complements recent observations that the spatial frequency of WMH among healthy older adults is

Figure 3. Example of regional white matter hyperintensity (WMH) quantification for one subject. Upper left: raw T2-weighted FLAIR image. Upper right and lower two: WMH labeled with “hottest” colors indicating most hyperintense voxels. Colors correspond to cerebral lobes (green: frontal, brown: parietal, dark green: temporal, blue: occipital, mauve: cerebellum). FLAIR, fluid attenuated inverse recovery
greater in regions with lower normative perfusion values.\textsuperscript{46} We also showed that, among an epidemiological cohort of nondemented older adults, WMH were associated with chronological age and vascular risk factors\textsuperscript{37} and were most severe among adults with the highest absolute blood pressure and blood pressure fluctuation over a 3-year period (Brickman et al, unpublished). These observations lend further support that diminished perfusion and perhaps compromised cerebral autoregulation increase the risk for WMH development.

### The role of white matter hyperintensities in cognitive aging

Consistent observations of increasing WMH severity and variability with aging supports ongoing interest in their clinical or cognitive correlates (see ref 13). Most investigations of the cognitive correlates of WMH burden have been cross-sectional analyses among nondemented older adults, and few have considered regional specificity. Based on these studies, there is emerging evidence that the severity or volume of WMH is one source of the cognitive decline that is typical of normal aging.\textsuperscript{38} In one of the earlier syntheses of the cognitive correlates of WMH in aging, a quantitative review showed that the extent of WMH is associated particularly with poorer performance on tasks of executive functioning and processing speed, but not with fluid or crystallized intelligence or fine motor functioning.\textsuperscript{39} The results are consistent with a more recent quantitative meta-analysis, which also showed that the severity of WMH burden is associated with poorer performance on speeded tasks of executive function in both healthy elderly and in individuals with a history of cardiovascular disease.\textsuperscript{40}

WMH may affect cognitive functioning through disruption of intracerebral connectivity, compromising efficient neuronal communication.\textsuperscript{41} Thus, regional specificity of the distribution of these lesions may be associated with unique cognitive profiles. The prefrontal cortex and its extensive cortical-cortical and cortical-subcortical connectivity is thought to play a central role in executive functioning,\textsuperscript{38,42} and damage to these areas may account for the predominant pattern of executive functioning decline in aging. Indeed, the age-associated changes in executive functioning appear to be partially mediated by increased burden of WMH distributed in frontal lobe regions\textsuperscript{43,44} and WMH distribution in prefrontal regions among older adults negatively impacts functional activity in the same region.\textsuperscript{45} Despite cross-sectional observations of associations between frontal WMH and executive functioning, there has been a paucity of studies examining the longitudinal progression of WMH and associated changes in cognitively normal elderly. Studies have found that increasing global WMH over a 4- or 5-year period, but not lacunar infarcts, are associated with worsening executive abilities and speeded abilities.\textsuperscript{46-48}

Taken together, the culmination of findings establish that WMH are common in normal aging, progress substantially, and suggest that this progression, particularly in anterior regions, may partially account for typical age-associated decline in executive abilities.

### The role of white matter hyperintensities in Alzheimer’s disease

More recently, the question of whether WMH play a unique role in the presentation or pathogenesis of AD has emerged. WMH are more prevalent and severe in AD patients compared with nondemented, but demographically similar older adults.\textsuperscript{17,49-51} Studies that have examined regional distribution of WMH show more posterior involvement, including posterior periventricular regions and posterior corpus callosum\textsuperscript{20,52} and increasing caudal involvement with more severe cognitive impairment.\textsuperscript{20} Interestingly, brain regions where WMH are most severe in AD colocalize to the distribution of AD pathology and areas showing the greatest metabolic dysfunction in AD.\textsuperscript{53} In our community-based study, we showed a selective association between WMH burden and diagnosis of amnestic mild cognitive impairment (MCI)—those at greatest risk for development of AD—but not nonamnestic MCI.\textsuperscript{54} Preliminary examination of the regional distribution showed that WMH burden in parietal lobes discriminated best among those with amnestic MCI, non amnestic MCI, and controls, again suggesting that a posterior distribution may be specific to or linked pathologically to AD.

Whether evaluation of neuroimaging data at one point in time has prognostic value for future clinical course or progression to AD remains an important question. Older adults who are not demented but who have increased WMH burden are at higher risk for the development of AD\textsuperscript{55-57} and MCI.\textsuperscript{58} We sought to determine whether baseline measurement of WMH severity and global atrophy, as a proxy of overall disease burden, predict future cognitive decline among patients with AD.\textsuperscript{59} Using a series
of generalized estimating equation models, we demonstrated that the degree of baseline atrophy, the severity of WMH, and their interaction predicted the rate of cognitive decline. That is, greater severity of baseline atrophy and greater severity of baseline WMH were associated with faster rates of cognitive decline in AD and the interaction of the two variables suggest synergy between cerebrovascular disease and overall disease burden. These findings are consistent with others showing that the presence of both elevated amounts of atrophy and high WMH burden is more associated with AD than the presence of both elevated amounts of atrophy and greater severity of WMH, and their interaction predicted the rate of cognitive decline in AD and the interaction of the two variables suggest synergy between cerebrovascular disease and overall disease burden.

Direct examination of the association between centrally deposited Aβ and WMH provides another approach towards understanding a link between WMH or microvascular disease and AD pathology, and two general classes of studies have begun to address this issue precisely. First, cerebral amyloid angiopathy (CAA) is present in the vast majority of patients with AD at autopsy. Cerebral amyloid angiopathy reflects the deposition of Aβ in cerebral arterioles and is manifested as lobar cerebral microbleeds, best visualized in vivo on T2*-weighted gradient-echo MRI. Importantly, WMH are more frequent in the presence of microbleeds or clinical CAA and those with clinical CAA show a progressive increase in WMH, suggesting that CAA may cause progressive white matter changes. A recent report noted that microbleeds had a lobar distribution in 92% of patients with AD and were predominantly distributed in posterior regions. The presence and frequency of microbleeds among AD patients predicted the severity of WMH, which was colocalized in parieto-occipital distributions. Given the studies showing colocalization among WMH, microbleeds, and the pathological distribution of AD, it is possible that the greater posterior distribution of WMH in AD could reflect the specific contribution of CAA, but future studies will need to address this possibility specifically.

Second, one of the most exciting developments in neuroimaging has been the ability to label in vivo central amyloid depositions using a carbon-11-labeled, lipophilic derivative of thioflavin-T, termed “Pittsburgh Compound B” or simply “PIB.” PIB can detect amyloid pathology even among nondemented individuals and has been associated with Aβ42 levels in cerebrospinal fluid. More recently, two reports demonstrated that PIB also reliably labels vascular deposition of Aβ and is able to discriminate patients with clinically diagnosed cerebral amyloid angiopathy from those with AD. Thus, while the culmination of studies reviewed above suggest that WMH are purely ischemic, resulting from systemic or variable hypoperfusion, multimodal neuroimaging, and pathological examination would suggest a more heterogeneous
profile, perhaps with an amyloidogenic source of WMH distributed in posterior cortex among individuals with and at risk for AD. The studies highlight the potential importance of both parenchymal and vascular β amyloid in the pathogenesis of AD and suggest that the two are mechanistically linked. It will be critical to extend this line of research and determine the association between regional distribution of WMH, cerebral microbleeds, and PIB uptake among individuals with and without AD, and future studies should undertake this effort among large samples of community-based individuals.

Current status of white matter hyperintensities and future directions

Structural neuroimaging studies of aging and dementia have highlighted the importance of WMH in normal age-associated cognitive loss and in AD. The prevailing view of WMH is that they represent small-vessel ischemic cerebrovascular disease secondary to perfusion abnormalities. Recent work implicates their involvement in the presentation and pathogenesis of AD and points to a potential amyloidogenic source, particularly when they are distributed in posterior cortex. There are several consistent findings regarding cerebrovascular disease in the context of AD that have emerged, with several etiological possibilities. First, the presence of small-vessel cerebrovascular disease among patients with AD is the norm, not the exception. Second, patients who have coexisting AD and small-vessel cerebrovascular disease have more severe cognitive impairment than those having either alone and brain imaging markers of each seem to interact synergistically to impact longitudinal cognitive course. Third, cerebrovascular disease and AD share common risk factors. From an etiological perspective, AD and cerebrovascular disease may be independent, but share common risk factors. Similarly, cerebrovascular disease may represent an independent pathology that lowers the threshold for clinical expression of AD or contributes independently to cognitive dysfunction. On the other hand, cerebrovascular disease may be in the causal pathway for development of AD or interact synergistically with AD pathology. These possibilities are not mutually exclusive, but given the overlap in risk factors, prevalence of cerebrovascular disease in AD, involvement of both vascular and parenchymal forms of β amyloid, and interactions between the two on clinical presentation, there is preliminary evidence of etiological or mechanistic overlap.

It is clear that future work should focus on disentangling these etiological possibilities in order to better inform treatment and prevention strategies. Longitudinal studies comprising community samples and incorporating multimodal neuroimaging modalities will help establish cause-effect relationships. For example, while associations between WMH burden and AD have been observed, the questions of whether the progression or accumulation of WMH leads to AD needs to be addressed. Similarly, as acquisition and analytic techniques continue to evolve, investigators need to follow suit and become more precise in the questions being asked and the nature of the neuroimaging signal under study. WMH are important radiological correlates of cognitive aging, but most likely represent heterogeneous pathology that requires further elucidation through advanced imaging techniques and combined methodological approaches.

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La disfunción cerebral objetivable que acompaña el envejecimiento puede tener un efecto devastador en las capacidades cognitivas e intelectuales. Un porcentaje significativo de adultos mayores experimentan una marcada declinación cognitiva que afecta negativamente las actividades funcionales. Esos individuos cumplen los criterios diagnósticos clínicos para demencia, la cual se atribuye comúnmente a la Enfermedad de Alzheimer (EA). La neuroimagenología estructural, incluida la resonancia magnética (RM), ha contribuido significativamente a la comprensión de los cambios morfológicos y aquéllos relacionados con alguna patología que pueden estar a la base del cambio cognitivo normal y el asociado con alguna enfermedad durante el envejecimiento. Las hiperintensidades de la sustancia blanca (HSB), que se distribuyen en parches de hiperintensidad de señal en las secuencias potenciadas en T2 están entre los hallazgos más frecuentes de la neuroimagenología estructural en los adultos mayores. En los últimos años, la HSB se ha considerado un potente correlato radiológico de la declinación cognitiva. Los estudios sugieren que la HSB distribuida en las regiones cerebrales anteriores se relaciona con la declinación de las habilidades ejecutivas y es típica del envejecimiento normal; en cambio, la HSB distribuida en regiones cerebrales más posteriores es común en la EA. Aunque los estudios epidemiológicos, observacionales y patológicos sugieren que la HSB puede tener un origen isquémico y ser causada por hipo-perfusion constante o variable, ha aparecido evidencia que sugiere que también puede reflejar depósito vascular de β-amiloido, particularmente cuando está distribuida en áreas posteriores y se presenta en pacientes con EA. Los hallazgos de la literatura destacan la potencial contribución de la enfermedad cerebral vascular de pequeño vaso a la patogénesis de la EA y sugieren una interacción mecanística, pero se requiere a futuro de estudios longitudinales que utilicen varias formas de neuroimágenes para una total comprensión del complejo papel de la HSB en la EA.

Les dysfonctions cérébrales objectivées liées à l’âge peuvent avoir un effet dévastateur sur les capacités cognitives et intellectuelles. Un pourcentage significatif d’adultes âgés subissent un déclin cognitif brutal qui retenti défavorablement sur les activités fonctionnelles. Ces personnes présentent des critères diagnostiques cliniques de démence, habituellement rapportés à la maladie d’Alzheimer (MA). La neuro-imagerie anatomique, dont l’imagerie par résonance magnétique (IRM), nous a beaucoup aidés à comprendre les modifications morphologiques et pathologiques qui pourraient sous-tendre les changements cognitifs du vieillissement normal et pathologique. Les hyperdensités de la substance blanche (HSB), qui se présentent sous la forme de petites taches éparse apparaissant à l’IRM en hypersignal en séquence pondérée en T2, sont très fréquemment observées en neuro-imagerie anatomique chez les sujets âgés. Ces dernières années, les HSB ont été reconnues comme étant des signes radiologiques fiables du déclin cognitif. Des études suggèrent que les HSB localisées dans la région antérieure du cerveau seraient liées au déclin des aptitudes exécutives typique du vieillissement normal, alors que les HSB situées dans les régions plus postérieures sont fréquentes dans la MA. Bien que des études épidémiologiques, observationnelles et pathologiques suggèrent que les HSB puissent être d’origine ischémique et provoquées par une hypo-perfusion permanente ou variable, il semble maintenant qu’elles puissent aussi être le signe d’un dépôt vasculaire de substance bêta-amyloïde, surtout lorsqu’il est localisé dans les régions postérieure et présent chez les patients atteints de MA. Les résultats de la littérature soulignent l’éventuelle contribution de la pathologie cérébrovasculaire des petits vaisseaux à la pathogenèse de la MA et suggèrent une interaction mécanistique. Mais il faudra encore d’autres études longitudinales aux modalités d’imagerie multiples pour comprendre parfaitement le rôle complexe des HSB dans la MA.
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