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Regional white matter hyperintensities: aging, AD risk, and cognitive function

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Abstract

White matter hyperintensities (WMH) of presumed vascular origin as seen on T2-weighted fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), are known to increase with age and are elevated in Alzheimer's disease (AD). The cognitive implications of these common markers are not well understood. Previous research has primarily focused on global measures of WMH burden and broad localizations that contain multiple white matter tracts. The aims of this study were to determine the pattern of WMH accumulation with age, risk for AD, and the relationship with cognitive function utilizing a voxel-wise analysis capable of identifying specific white matter regions. Three hundred and forty-nine participants underwent T1-weighted and high-resolution T2FLAIR MRI and neuropsychological testing. Increasing age and lower cognitive speed and flexibility (a component of executive function), were both significantly associated with regional WMH throughout the brain. When age was controlled, lower cognitive speed and flexibility was independently associated with WMH in the superior corona radiata. APOE4 and parental family history of AD were not associated with higher burden of WMH. The results contribute to a larger body of literature suggesting that white matter measures are linked with processing speed, and illustrate the utility of voxel-wise analysis in understanding the effect of lesion location on cognitive function.

Keywords

white matter hyperintensities; aging; processing speed; cognition; MRI

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Disclosure Statement

None of the authors have actual or potential conflicts of interest.

Introduction

White matter hyperintensities (WMH) of presumed vascular origin, as seen on T2-weighted fluid attenuated inversion recovery (FLAIR) MRI, are common features of the aging brain (de Leeuw, de Groot et al. 2001). By the fifth decade of life, approximately 50% of people will have some WMH (Wen, Sachdev et al. 2009), while in healthy adults in their mid-sixties, it's likely that most will have some degree of WMH as found using T2-weighted imaging (Wen and Sachdev 2004). The underlying cause of these hyperintense regions is thought to be small vessel disease, and accordingly, hypertension and older age are most consistently associated with an increasing burden of WMH (Basile, Pantoni et al. 2006).

Despite the fact that WMH denote localized white matter damage, the associated cognitive changes and risk conferred by WMH for pathological cognitive decline remain incompletely characterized. Several studies suggest a link between WMH and cognitive function even in healthy aging (de Groot, de Leeuw et al. 2000; Gunning-Dixon and Raz 2003; Van Petten, Plante et al. 2004; Soderlund, Nilsson et al. 2006; Frisoni, Galluzzi et al. 2007; Smith, Salat et al. 2011) but other studies have failed to find a link in healthy older adults [for a review see Ferro and Madureira (2002)]. While not considered a defining feature of Alzheimer's disease (AD), WMH are elevated in AD and mild cognitive impairment (MCI) (Yoshita, Fletcher et al. 2006; Cuenco, Green et al. 2008). In AD patients, higher baseline WMH are associated with a greater increase in amyloid- β deposition, potentially due to small vessel disease and subsequently impaired amyloid- β clearance (Grimmer, Faust et al. 2012). WMH also appear to play a role in risk for developing AD; a meta-analysis showed that WMH are a risk factor for AD within population studies (Debetto and Markus 2010) and parietal WMH are associated with the risk of incident AD in older adults (Brickman, Provenzano et al. 2012). Whether WMH could be considered a feature of early stage AD, or a result of AD pathological processes is still unknown, and the literature linking WMH to AD risk factors is mixed. Some studies have found elevated WMH in Apolipoprotein E ϵ 4 (APOE4) carriers (de Leeuw, Richard et al. 2004; Lunetta, Erlich et al. 2007), while Biffi et al. (2010) did not find a relationship between APOE4 status and WMH in the Alzheimer's Disease Neuroimaging Initiative cohort. The effect of APOE4 may not be specific to AD, as it is also a risk factor for cerebrovascular disease. Parental family history of AD is another well-know risk factor for AD; however, Debetto et al. (2009) did not find an effect of parental family history on lesion burden, despite the fact that this risk factor has been linked with white matter alterations as detected with diffusion tensor imaging (DTI) in another study (Bendlin, Ries et al. 2010).

Differences among findings may be due to differences in the population under study, or differences in the way WMH are indexed. WMH in aging and AD have hitherto mainly focused on global lesion volume, e.g. Aggarwal, et al. (2010; Brickman, Siedlecki et al. 2011; Carmichael, Mungas et al. 2012), and broadly defined localization (2010; Guzman, Carmichael et al. 2013).. Given that both aging and AD are associated with regional patterns of white matter change as detected using DTI or volumetric analysis (Good, Johnsrude et al. 2001; Li, Pu et al. 2008; Alves, O'Dwyer et al. 2012), more research may be needed that considers WMH in specific brain locations.

Voxel-wise analysis in which variables of interest can be used to predict WMH throughout the whole brain across a large number of participants can provide regional information with high spatial resolution. Utilizing automated segmentation may also provide a solution to the variability in WMH rating approaches used across laboratories. Largely due to challenges in automated lesion segmentation, voxel-wise approaches to analyzing WMH still rare in the literature. Rostrup, et al. (2012) found differing spatial distribution of WMH with several risk factors for WMH, but did not investigate associations with cognitive symptoms. An

elegant study by Smith, et al. (2011) reported a relationship between frontal, posterior, and periventricular white matter lesion burden and executive function. In that same study, frequency of lesions in many of the same posterior and periventricular regions was associated with poorer episodic memory function. The participants in that study were all over the age of 65 and were cognitively normal or diagnosed with MCI or mild dementia. Whether voxel-wise localization of WMH with age is associated with cognitive function or AD risk factors in asymptomatic adults, is relatively unknown.

Thus, the aims of this study were to: (1.) determine the pattern of regional WMH found with increasing age; (2.) determine the extent to which regional WMH are associated with cognitive function; and (3.) assess the impact of parental family history and APOE4 genotype on regional distribution of WMH. In addition to regional analyses, secondary analyses also examined total WMH in order to compare with existing studies. We hypothesized that older age would be associated with higher regional WMH, especially in frontal brain regions, that regional burden would be linked to cognitive dysfunction, and that AD risk would be associated with higher frequency of WMH, especially in AD specific regions, including parietal and temporal lobes.

Methods

Participants

Three hundred and fifty-nine participants from the Wisconsin Registry for Alzheimer's Prevention (WRAP) underwent brain imaging as part of studies on memory, aging, and risk for AD. WRAP is a longitudinally followed cohort comprising participants who either have a family history of late onset AD or no family history of AD (Sager, Hermann et al. 2005). The majority of the WRAP participants are adult children of persons with AD who were evaluated at the Memory Assessment Clinic at the University of Wisconsin-Madison or satellite memory assessment clinics affiliated with the Wisconsin Alzheimer's Institute, and other participants who learned about the study from educational presentations, health fairs, newsletters, or word of mouth. A positive family history was defined as having one or both parents with autopsy-confirmed or probable AD as defined by NINCDS-ADRDA research criteria (McKhann, Drachman et al. 1984) and reviewed by a multidisciplinary diagnostic consensus panel. Absence of family history of AD required that the father survive to at least age 70 and the mother to age 75 without incurring a formal diagnosis of dementia or exhibiting cognitive deterioration. The inclusion criteria for this imaging study consisted of: normal cognitive function determined by neuropsychological evaluation (MMSE ≥ 25), no contraindications for magnetic resonance imaging (MRI) and a subsequent normal MRI scan, no current diagnosis of major psychiatric disease or other major medical conditions (e.g., myocardial infarction, or recent history of cancer), and no history of head trauma, stroke or transient ischemic attack. All participants underwent MRI and neuropsychological testing. Brain images were reviewed by a neuroradiologist to exclude infarcts and other abnormalities. Ten participants were excluded because of abnormal radiological findings from the reviewing radiologist, leaving 349 participants. Demographic information for this sample is presented in Table 1. The University of Wisconsin Institutional Review Board approved all study procedures and each participant provided signed informed consent before participation.

Cognitive testing

As part of their participation in WRAP, participants received at least one comprehensive neuropsychological assessment (Sager, Hermann et al. 2005). For participants with multiple assessments, factor scores were used from the testing date in closest proximity to the MR scan. On average, neuropsychological testing occurred within nine months of the MRI scan

($SD = 5.3$ months). We analyzed four cognitive factor scores that were determined from a factor analytic study of the WRAP neuropsychological battery and adapted from work published in Dowling et al.(2010). Factor scores represented cognitive domains known to change with age: Immediate Memory, Verbal Learning & Memory, Working Memory, and Speed & Flexibility. The individual tests which loaded onto the factors were as follows: Immediate Memory - Rey Auditory Verbal Learning Test (RAVLT) Trials 1 and 2 (Spreen and Strauss 1998); Verbal Learning & Memory - RAVLT Trials 3–5 and Delayed Recall Trial; Working Memory - Wechsler Adult Intelligence Scale – 3rd edition Digit Span, Arithmetic, and Letter-Numbering Sequencing subtests (Wechsler 1997); Speed & Flexibility - Stroop Test interference trial (Trenerry 1989), and Trail Making Test A and B(Reitan and Wolfson 1993). Factor scores from all waves were standardized around WRAP baseline data.

The Speed and Flexibility factor score was unavailable for eight participants (five were colorblind and unable to perform the Stoop test, and Trail Making Tests were unavailable for three participants due to tester error). These eight participants were excluded for all analyses involving the Speed and Flexibility factor score.

Brain Imaging Acquisition

MR scanning was performed on a General Electric 3.0 Tesla Discovery MR750 (Waukesha, WI) MRI system with an 8-channel head coil and parallel imaging (ASSET).

A T1-weighted volume was acquired in the axial plane with a 3D fast spoiled gradient-echo (3D FSPGR) sequence using the following parameters: TI = 450 ms; TR = 8.1 ms; TE = 3.2 ms; flip angle = 12°; acquisition matrix = 256 × 256 mm, FOV = 256 mm; slice thickness = 1.0 mm.

A 3D T2-weighted fluid attenuated inversion recovery (FLAIR) sequence was acquired in the sagittal plane using the following parameters: TI = 1868 ms; TR = 6000 ms; TE = 123 ms; flip angle = 90°; acquisition matrix = 256×256, FOV = 256 mm; slice thickness = 2.0 mm, no gap, yielding a voxel resolution of 1 mm × 1 mm × 2 mm.

ICV calculation

Intracranial volume (ICV) was calculated to scale for differences in head size in the WMH analyses using a “reverse brain masking” method (Keihaninejad, Heckemann et al. 2010). First, summing the gray, white and CSF ICBM probability maps created an ICV probability map. Then, the inverse deformation field resulting from unified segmentation on each participant image was applied to the ICV probability map, in order to produce an ICV mask in native space. A threshold of 90% was applied to this participant specific ICV probability map and the total volume was extracted. Total and regional analyses were adjusted for ICV in order to control for the variability in brain size.

WMH segmentation

Total volume of WMH was calculated using the Lesion Segmentation Tool (LST) version 1.2.2 in SPM8 (Schmidt, Gaser et al. 2012). Utilizing automated segmentation provides the advantage of high reliability. The toolbox is open source and utilizes T1-weighted and T2FLAIR images for lesion segmentation. Lesions are seeded based on spatial and intensity probabilities from T1 images and hyperintense outliers on T2FLAIR images. The initial threshold was set at 0.30 and is used to create the binary conservative lesion belief map from the gray and white matter lesion belief maps. Next, a growth algorithm grows these seeds from the conservative lesion belief map toward a probabilistic liberal lesion belief map from gray matter, white matter, and cerebral spinal fluid belief maps. Lastly, we used a threshold

of 1.00 on the resulting lesion belief map to remove any voxels that have a lower probability of being a lesion. Schmidt et al. (2012) demonstrated high agreement ($R^2 = 0.94$) between LST and manual tracing in a sample of patients with multiple sclerosis and controls using a version of the software that utilized only the gray matter belief map to seed the algorithm. We found that using the gray and white matter belief maps to seed the algorithm produced more accurate segmentation of lesions in our sample. The resulting total volume of WMH was divided by ICV and multiplied by 100 to give a ratio (WMHr) in units of percent of ICV, which was used for analysis using total lesion volume. In accordance with recently published consensus standards for research into small vessel disease in aging (Wardlaw, Smith et al. 2013), all final segmentation maps were visually inspected.

For voxel-wise WMH analysis, probability lesion belief maps were normalized to Montreal Neurological Institute (MNI) space and smoothed with a 12mm Gaussian kernel. Since the results were in MNI space, we utilized the ICBM DTI-81 white matter atlas (<http://www.loni.ucla.edu/Atlases>) to identify specific regions of association.

Finally, a constant of one was added and a log transformation was applied to WMHr values and lesion probability maps in order to normalize the distribution of WMH.

Statistical Analyses

Statistical tests were considered significant at $p < 0.05$. Voxel-wise statistics in SPM8 were corrected for multiple comparisons with a familywise error rate correction (FWE). Voxel-wise analyses were restricted to white matter using an explicit mask made by thresholding the ICBM Tissue Probabilistic Atlases white matter map at 0.30. Results were cluster thresholded at >20 voxels to exclude very small clusters and increase anatomical plausibility.

1. Association between age and total and regional WMH

To test the hypothesis that global WMHr increased with age, linear multiple regression was used in IBM SPSS version 20.0 (Chicago, IL), assessing the significance of age (independent variable), controlling for sex on WMHr (dependent variable). The multiple regression model was used in SPM8 to determine regional correlations between age and lesion probability on a voxel-wise basis. Age was the predictor variable and the voxel values of the smoothed lesion probability belief maps were the dependent variable. Sex and ICV were entered as covariates.

2. Association between cognition and total and regional WMH

To test the hypothesis that cognitive functioning decreases with increasing WMHr, linear multiple regression analysis was used. Cognitive factor scores (dependent variable) and total WMHr (independent variable) were entered into the analysis, adjusting for the effects of age, sex, and years of education. Multiple regression in SPM8 was used to test linear regional correlations between cognitive factor scores and WMH probability across the whole brain (voxel-wise), controlling for age, sex, years of education, and ICV as covariates. Age was used as a covariate because of the strong association between age and both cognitive function and WMH and the possibility of spurious correlations. Since WMH are believed to underlie declines in age related cognitive function, a voxel-wise model was performed without controlling for age.

3. Associations between WMH and Alzheimer's risk (APOE4 and parental family history of AD)

To test the hypothesis that APOE4 carriage and parental family history of AD incurs higher total WMHr, ANOVA was used with APOE4 and parental family history as the independent variables and WMHr as the dependent variable, controlling for the effects of age, sex, and years of education. The two-sample t-test design was used in SPM8 to test for regional group differences between APOE4 carriers and non carriers and between those with a parental family history of AD and those without. Age, sex, years of education and ICV were entered as covariates.

Results

1. Association between age and total and regional WMH

In a multiple regression model controlling for sex, age was a significant predictor of global WMHr, $\beta = 0.39$, $t(346) = 7.8$, $p < 0.001$ (Figure 1). Based on the possibility of a non-linear pattern of white matter change with age, we also fit a non-linear slope; the quadratic function had an $r(346) = 0.39$ and did not explain more variance than the linear fit.

Controlling for sex and ICV, a voxel-wise analysis revealed a linear relationship between increasing age and increasing lesion probability in large areas of bilateral WM including all portions of the corpus callosum, the fornix, the superior cerebellar peduncles, the cerebral peduncles, all portions of the internal capsule, the anterior, posterior, and superior corona radiata, the posterior thalamic radiation, the external capsule, the cingulum, the superior longitudinal fasciculus, and the superior and inferior fronto-occipital fasciculus. (Figure 2 & Table 2).

2. Association between cognition and total and regional WMH

Speed and Flexibility was the only cognitive measure that was associated with global WMHr controlling for age, sex, and years of education, $\beta = -0.13$, $t(336) = -2.5$, $p = 0.01$ (Figure 3). Controlling for sex and years of education, age significantly predicted the Speed and Flexibility factor score, $\beta = -0.41$, $t(337) = -8.3$, $p < 0.001$.

The regional voxel-wise analysis revealed that lower Speed and Flexibility factor score was associated with higher lesion probability in many of the same regions observed with age, controlling for sex, years of education, and ICV (Figure 4a & Table 2). Qualitatively, the relationship between age and WMH probability extended over a greater portion of WM compared to the Speed and Flexibility result map, which lacked significant associations in the splenium and tapetum of the corpus callosum, the fornix, the cerebellar and cerebral peduncles, the posterior limb of the internal capsule, and the inferior fronto-occipital fasciculus. Considering that WMH and Speed and Flexibility are both strongly related to age, this result not controlling for age most likely contains effect from confounds also associated with age. When age was controlled, Speed and Flexibility was correlated with WMH in the body of the corpus callosum, bilateral areas of the anterior and superior corona radiata, and the right cingulum (Figure 4b & Table 2). Since it is believed that WMH may be a neurological substrate responsible for some portion of age related cognitive decline, controlling for age most likely removes some of the variance shared by age and Speed and Flexibility in this result.

3. Associations between WMH and Alzheimer's Risk (APOE4 and parental family history of AD)

Parental family history of AD did not predict WMHr controlling for age, sex, and years of education, $F(1, 344) = 0.05$, $p = 0.83$. Controlling for the same variables, APOE4 carrier

status did not predict WMHr, $F(1, 344) = 0.19, p = 0.66$. Using the same models in SPM8, there were no regional associations between WMH probability and APOE4 or parental family history of AD.

Discussion

The goals of this study were to determine the regional localization of WMH with age, to determine the effect of WMH on cognitive function in the context of aging, and assess the effect of Alzheimer's risk on WMH in a large sample of healthy late middle aged participants. We observed that increasing age and lower cognitive speed and flexibility are strongly associated with WMH throughout white matter. Furthermore, the factor score representing speed and flexibility was independently associated with WMH in an area containing portions of the superior corona radiata bilaterally, the anterior corona radiata bilaterally, and the right cingulum, where higher WMH probability was associated with lower cognitive performance. The Speed and Flexibility factor score reflects processes that are considered under the broad category of executive function. Alzheimer's risk was not associated with regional lesion burden in this study.

Our results are consistent with and extend the established literature, which suggests that WMH are often associated with decreasing executive functioning and speed of processing. The localization of correlations between cognitive speed and flexibility and WMH in this study is consistent with studies that have shown a relationship between visually rated periventricular WMH and speed of processing and executive function (de Groot, de Leeuw et al. 2000; Soderlund, Nilsson et al. 2006). Using voxel-wise analysis, Smith et al. (2011) observed that frontal and periventricular WMH are associated with lower executive functioning in older participants with AD, MCI, and normal cognition. Using tracing methods in a population with a similar mean age to our sample, Raz et al found a relationship between frontal WMH, including periventricular regions, and executive function (Raz, Rodrigue et al. 2003). Other studies have found impacts on executive function and processing speed when looking across several brain regions; in a study of patients with subcortical ischemic vascular disease and AD, Tullberg et al found that WMH contribute to impairments in executive function regardless of lesion location (Tullberg, Fletcher et al. 2004). Using lobar parcellation of the brain and a region of interest approach, Murray et al. found that higher WMH in all regions except the occipital lobe was associated with lower executive function (Murray, Senjem et al. 2010).

We did not find a relationship between WMH and memory. Several other studies have observed an association between memory measures and WMH (Gunning-Dixon and Raz 2000; Van Petten, Plante et al. 2004; Smith, Salat et al. 2011; Carmichael, Mungas et al. 2012), and indeed, WMH have been found to underlie episodic memory deficits, even in the absence of hippocampal atrophy (Nordahl, Ranganath et al. 2005). The current study focused on a relatively healthy and well-educated population (with approximately 16 years of education), which may explain why effects were found for the Speed and Flexibility factors score, but not other aspects of cognitive function. Factors such as brain and cognitive reserve have been noted to mitigate the impact of pathology on cognition (Brickman, Siedlecki et al. 2011). Other factors that may play a role in differing outcomes include age and disease status, WMH rating methods, and the choice of neuropsychological tests. Carmichael et al. found a relationship between WMH burden and both executive and memory function when examining participants who ranged in cognitive function from healthy to demented (Carmichael, Mungas et al. 2012), however, when controlling for diagnostic status, the relationship with memory was trending, but not significant. Bunce et al. studied a relatively young population of community-dwelling adults aged 44 to 48 years, and found that temporal WMH were associated with memory, however in this case the task

was non-verbal (face recognition), and only present in men (Bunce, Anstey et al. 2010). In a primarily male population studied in the SMART-MR study, WMH burden interacted with brain volume measures to produce lower executive function, but did not have an effect on memory function (Muller, Appelman et al. 2011). Likewise, in a study which assessed the contribution of childhood IQ on later-life cognitive function in an older, but non-demented sample, Valdés Hernández et al. found that WMH have an incremental effect on reducing general cognitive ability and processing speed, but not memory (Valdes Hernandez, Booth et al. 2013), and results from the Framingham Heart study also point toward a relatively stronger relationship between WMH and frontal lobe based cognitive tasks compared to medial temporal lobe based memory tests (Au, Massaro et al. 2006). A recent study in a cognitively healthy older sample found that memory function was affected by amyloid burden, while executive function was more closely associated with WMH (Hedden, Mormino et al. 2012). While episodic memory function can be clearly impacted by WMH burden, at least one study suggests that this effect is mediated by executive functioning (Parks, Iosif et al. 2011). Given that the participants in the current study—while younger—showed an effect of WMH on subcomponents of executive function, suggests that effects on memory may be impending as the WRAP sample ages, or as age-related diseases manifest. Longitudinal work in this area indicates that WMH continue to evolve over time with significant consequences for cognitive function (Maillard, Carmichael et al. 2012).

The mainly periventricular distribution of WMH with increasing age in this study is consistent with the voxel-wise WMH age distribution found in Rostrup et al. (2012), which studied an older population. WMH appear to accumulate in periventricular and deep white matter near the precentral gyrus. A voxel-wise study using diffusion tensor imaging (DTI) from our group which included participants from the WRAP cohort showed a relationship between lower fractional anisotropy in the superior corona radiata and poorer performance on complex attention and set shifting as measured by Trails B (Bendlin, Fitzgerald et al. 2010). Additional DTI studies have also indicated that altered measures of white matter microstructure in the superior corona radiata are associated with poorer performance in task switching and processing speed (Sasson, Doniger et al. 2012; Leunissen, Coxon et al. 2013). A tractography study performed by Leunissen et al. (2013) showed that injury to fibers of the superior corona radiata—which connect the basal ganglia and thalamus to superior frontal gyrus and supplementary motor area—contributes to deficits in task switching. They point to an emerging body of evidence that cortico-subcortical damage may cause executive dysfunction through a lack of cognitive control (2013). The results of the current study, which found that WMH probability in the superior corona radiata was associated with speed and flexibility independently of age (Figure 4b), provides further support that portions of the superior corona radiata play a role in cognitive speed and flexibility.

We did not find a relationship between WMH and APOE4 or parental family history of AD. Our results concur with some studies that have also failed to find a link (DeBette, Wolf et al. 2009; Biffi, Anderson et al. 2010). In studies that have found a relationship between APOE4 and WMH, the participants were older than the sample in the current study (de Leeuw, Richard et al. 2004; Lunetta, Erlich et al. 2007) suggesting that APOE4 may be associated with WMH but only at an older age. Perhaps providing more information on the link between white matter health and AD risk, several studies have shown that the APOE4 effect on white matter microstructure as measured by DTI often interacts with age, such that a greater APOE4 effect is observed in older age (Nierenberg, Pomara et al. 2005; Persson, Lind et al. 2006; Smith, Chebrolu et al. 2010; Ryan, Walther et al. 2011).

This study has a few limitations that should be noted. This study is cross-sectional and longitudinal studies are needed to understand the temporal relationship between cognitive performance and the development of WMH (Wardlaw, Smith et al. 2013). The present

sample was recruited from an established registry for AD research enriched for family history of AD, potentially limiting the generalizability of these results. Further, it's important to note that while WMH account for some of the effects on cognitive function, (Soderlund, Nyberg et al. 2003; Vannorsdall, Waldstein et al. 2009), other aspects of neural health are important, as are the myriad of lifestyle and genetic factors that affect neural health and cognition. Finally, given the heterogeneous nature of WMH in aging, larger studies, different samples or different methods of assessing WMH could produce different results.

Conclusion

This large study examined the effects of age and AD risk on regional WMH, in addition to assessing the relationship between regional lesion burden and cognitive function in a large sample of healthy middle to older aged adults. The results suggest that white matter alterations partly underlie age-related changes in processing speed. Identifying factors associated with age-related decrease in processing speed is important, given that slowed processing speed has been implicated as the broad underlying deficit for other age-related cognitive declines (Salthouse 1996). The findings underscore the importance of considering lesion location for informing upon age-related cognitive decline.

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Figure 1. Residuals of white matter hyperintensity ratio [WMHr (% of intracranial volume)] after adjusting for sex as a function of age. $r(346) = 0.39$, $p < 0.001$.

Figure 2.

Areas of positive correlation with age on smoothed WMH probability belief maps controlling for intracranial volume and sex are displayed in cool colors (blue). The color bar indicates the t -value. FWE-correction, $p < 0.05$. Peak voxel coordinates, t -value, p -value, and cluster size are listed in Table 2.

Figure 3.

Residuals of WMHr after adjusting for age, sex, and years of education graphed as a function of cognitive factor scores. * significant $p < 0.05$

Figure 4.

(a) Areas of negative correlation with Speed and Flexibility factor score controlling for sex, intracranial volume, and years of education are shown in warm colors (yellow-orange). (b) Areas of negative correlation with Speed and Flexibility factor score controlling for age, sex, years of education, and ICV. FWE-correction, $p < 0.05$. The color bar indicates the t -value. Peak voxel coordinates, t -value, p -value, and cluster size are listed in Table 2.

Table 1Demographics (*N* = 349)

	<i>n</i> (%)	
female	238(68%)	
parental fam hist of AD	260(74%)	
ApoE4-carriers	131 (38%)	
diabetics	7 (2.2%)	
current smokers	17 (5%)	
history of hypertension	178 (51%)	
	<i>M</i> ± <i>SD</i>	range
Age	59.7 ± 6.4	[42 – 73]
Edu	16.2 ± 2.4	[12 – 20]
systolic BP	124 ± 16	[85 – 176]
diastolic BP	73 ± 9.5	[48 – 104]
WMH volume (mm ³)	11.7 ± 6.7	[2.3 – 45.4]
WMHr (% of ICV)	0.85 ± 0.49	[0.2 – 3.3]

Table 2

For each significant cluster, peak voxel MNI coordinates (x, y, z), *t*-statistic and *p*-value, and cluster size(k) are listed separately for each voxel-wise analysis.

Brain Region	x	y	z	k	t	p
WMH increase with age (Figure 2)						
R posterior thalamic radiation	33	-54	19	71551	8.13	<0.0001
WMH increase with lower Speed and Flexibility factor score (Figure 4a)						
R superior corona radiata	26	14	25	43,869	6.67	<0.0001
R middle occipital WM	27	-84	4	325	4.57	<0.0001
Body of the corpus callosum	-6	-22	22	296	4.38	<0.0001
L medial frontal WM	-12	-21	58	90	4.35	<0.0001
WMH increase with lower Speed and Flexibility factor score independent of age (Figure 4b)						
L superior corona radiata	-27	5	34	1,838	4.97	<0.0001
R superior corona radiata	28	17	28	726	4.87	<0.0001