ELSEVIER

Regional white matter hyperintensities: aging, Alzheimer's disease risk, and cognitive function

Alex C. Birdsill [a,b], Rebecca L. Koscik [c], Erin M. Jonaitis [c], Sterling C. Johnson [a,b], Ozioma C. Okonkwo [a,b], Bruce P. Hermann [c], Asenath LaRue [c], Mark A. Sager [b,c], Barbara B. Bendlin [a,b,*]

[a] Geriatric Research, Education and Clinical Center (GRECC), William S. Middleton Memorial Veteran's Hospital, Madison, WI, USA
[b] Wisconsin Alzheimer's Disease Research Center, Department of Medicine, University of Wisconsin, Madison, WI, USA
[c] Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, USA

ARTICLE INFO

ABSTRACT

White matter hyperintensities (WMH) of presumed vascular origin, as seen on T2-weighted fluid attenuated inversion recovery magnetic resonance imaging, 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. A total of 349 participants underwent T1-weighted and high-resolution T2-weighted fluid attenuated inversion recovery magnetic resonance imaging 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. Apolipoprotein E ε4 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.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

White matter hyperintensities (WMH) of presumed vascular origin, as seen on T2-weighted fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), are common features of the aging brain (de Leeuw et al., 2001). By the fifth decade of life, approximately 50% of people will have some WMH (Wen et al., 2009), whereas in healthy adults in their mid-60s, it is 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 et al., 2006).

Despite the fact that WMH denotes localized white matter damage, the associated cognitive changes and risk conferred by WMH for pathologic cognitive decline remain incompletely characterized. Several studies suggest a link between WMH and cognitive function even in healthy aging (de Groot et al., 2000; de Leeuw et al., 2001; Frisoni et al., 2007; Gunning-Dixon and Raz, 2003; Smith et al., 2011; Soderlund et al., 2006; Van Petten et al., 2004) 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) (Cuenco et al., 2008; Yoshita et al., 2006). In patients with AD, higher baseline WMH are associated with a greater increase in amyloid-β deposition, potentially because of small vessel disease and subsequently impaired amyloid-β clearance (Grimmer 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 (Debette and Markus, 2010) and parietal WMH are associated with the risk of incident AD in older adults

* Corresponding author at: University of Wisconsin, School of Medicine and Public Health, J5/1M Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA. Tel.: +1 608 265 2483; fax: +1 608 265 3091.
  E-mail address: bbb@medicine.wisc.edu (B.B. Bendlin).

(Brickman et al., 2012). Whether WMH could be considered as a feature of early stage AD, or a result of AD pathologic processes is still unknown, and the literature linking WMH to AD risk factors is mixed. Some studies have found elevated WMH in Apolipoprotein E ε4 (APOE4) carriers (de Leeuw et al., 2004; Lunetta et al., 2007), although, Biffi et al. (2010) did not find a relationship between APOE4 status and WHM 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-known risk factor for AD; however, Debette 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 et al., 2010a, 2010b).

Differences among findings may be caused by differences in the population under study or differences in the way that WMH are indexed. WMH in aging and AD have so far focused mainly on global lesion volume (Aggarwal et al., 2010; Brickman et al., 2011; Carmichael et al., 2012) and broadly defined localization (Guzman 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 (Alves et al., 2012; Good et al., 2001; Li et al., 2008), 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. Using automated segmentation might also provide a solution to the variability in WMH rating approaches used across laboratories. Largely because of challenges in automated lesion segmentation, voxel-wise approaches to analyzing WMH are 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. All the participants in that study were older than 65 years 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 as follows: (1) to determine the pattern of regional WMH found with increasing age; (2) to determine the extent to which regional WMH are associated with cognitive function; and (3) to 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 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.

2. Methods

2.1. Participants

A total of 359 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 have either a family history of late-onset AD or no family history of AD (Sager et al., 2005). Most of the WRAP participants were 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 1 or both parents with autopsy-confirmed or probable AD as defined by National Institute of Neurological and Communicative Disorders, and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) research criteria (McKhann et al., 1984) and reviewed by a multidisciplinary diagnostic consensus panel. Absence of family history of AD required that the father survived 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 (Mini Mental State Examination ≥25), no contraindications for 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 reviews made by the 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.

2.2. Cognitive testing

As a part of their participation in WRAP, participants received at least 1 comprehensive neuropsychological assessment (Sager et al., 2005). For participants with multiple assessments, factor scores were used from the testing date in closest proximity to the MRI scan. On average, neuropsychological testing occurred within 9 months of the MRI scan (standard deviation [SD] = 5.3 months). We analyzed 4 cognitive factor scores that were determined from a factor analytic study of the WRAP neuropsychological battery and adapted from the work published in (Dowling et al., 2010). Factor scores represented cognitive domains known to change

Table 1
Demographics characteristics of patients (N = 349)

Characteristic	n (%)
Female	238 (68%)
Parental familial history of AD	260 (74%)
ApoE4 carriers	131 (38%)
Diabetic	7 (2.2%)
Current smoker	17 (5%)
History of hypertension	178 (51%)
	Mean ± SD (range)
Age	59.7 ± 6.4 (42–73)
Education	16.2 ± 2.4 (12–20)
Systolic blood pressure	124 ±16 (85–176)
Diastolic blood pressure	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)

Key: AD, Alzheimer's disease; WMH, white matter hyperintensity; WMHr, white matter hyperintensity ratio.

with age: Immediate Memory, Verbal Learning and Memory, Working Memory, and Speed and Flexibility. The individual tests which loaded onto the factors were as follows: Immediate Memory—Rey Auditory Verbal Learning Test Trials 1 and 2 (Spreen and Strauss, 1998); Verbal Learning and Memory—Rey Auditory Verbal Learning Test Trials 3–5 and Delayed Recall Trial; Working Memory—Wechsler Adult Intelligence Scale – third edition Digit Span, Arithmetic, and Letter-Numbering Sequencing subtests (Wechsler, 1997); Speed and 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 8 participants (5 were color blind and unable to perform the Stoop test, and Trail Making Tests were unavailable for 3 participants because of tester error). These 8 participants were excluded for all analyses involving the Speed and Flexibility factor score.

2.3. Brain imaging acquisition

MRI scan was performed on a General Electric 3.0 Tesla Discovery MR750 (Waukesha, WI, USA) MRI system with an 8-channel head coil and parallel imaging with Array Spatial Sensitivity Encoding Technique (ASSET).

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

A 3D T2FLAIR 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 x 256, FOV = 256 mm; slice thickness = 2.0 mm, no gap, yielding a voxel resolution of 1 mm x 1 mm x 2 mm.

2.4. Intracranial volume calculation

Intracranial volume (ICV) was calculated to scale for differences in head size in the WMH analyses using a "reverse brain masking" method (Keihaninejad et al., 2010). First, summing the gray, white, and cerebrospinal fluid (CSF) probability maps from The International Consortium for Brain Mapping (ICBM) 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, 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 to control the variability in brain size.

2.5. WMH segmentation

Total volume of WMH was calculated using the Lesion Segmentation Tool version 1.2.2 in SPM8 (Schmidt et al., 2012). Using automated segmentation provides the advantage of high reliability. The toolbox is open source and uses 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 CSF belief maps. Finally, 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 Lesion Segmentation Tool and manual tracing in a sample of patients with multiple sclerosis and controls with a version of the software that used 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 white matter hyperintensity ratio (WMHr) in units of percentage 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 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 space and smoothed with a 12-mm Gaussian kernel. Because the results were in Montreal Neurological Institute space, we used the ICBM DTI-81 white matter atlas (http://www.loni.ucla.edu/Atlases) Los Angeles, CA, to identify specific regions of association.

Finally, a constant of 1 was added and a log transformation was applied to WMHr values and lesion probability maps to normalize the distribution of WMH.

2.6. Statistical analyses

Statistical tests were considered significant at $p < 0.05$. Voxel-wise statistics in SPM8 were corrected for multiple comparisons with a family-wise 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 to increase anatomic plausibility.

2.6.1. 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, USA), 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 variables. Sex and ICV were entered as covariates.

2.6.2. 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. Because WMH are believed to underlie declines in age-related cognitive function, a voxel-wise model was performed without controlling for age.

2.6.3. Associations between WMH and AD 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, analysis of variance was
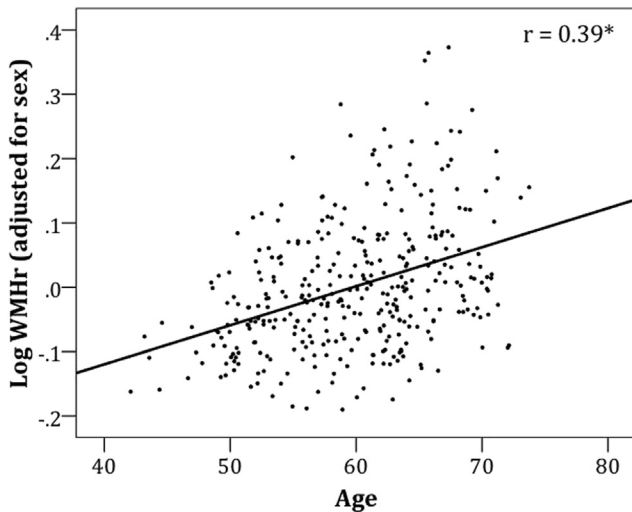
Fig. 1. Residuals of white matter hyperintensity ratio [WMHr (% of intracranial volume)] after adjusting for sex as a function of age. $r(346) = 0.39$, $p < 0.001$. Abbreviation: WMHr, white matter hyperintensity ratio.

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 2-sample t test design was used in SPM8 to test for regional group differences between APOE4 carriers and noncarriers and between those with a parental family history of AD and those without. Age, sex, years of education, and ICV were entered as covariates.

3. Results

3.1. Association between age and total and regional WMH

In a multiple regression model controlling for sex, age was a significant predictor of global WMHr, $\beta = 0.39$, $t(346) = 7.8$, $p < 0.001$ (Fig. 1). Based on the possibility of a nonlinear pattern of white matter change with age, we also fit a nonlinear 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 white matter (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. (Fig. 2 and Table 2).

3.2. Association between cognition and total and regional WMH

Speed and Flexibility factor score was the only cognitive measure that was associated with global WMHr controlling for age, sex, and years of education ($\beta = -0.13$, $t(336) = -2.5$, $p = 0.01$) (Fig. 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 (Fig. 4A & Table 2). Qualitatively, the relationship between age and WMH probability extended over a greater portion of WM compared with the Speed and Flexibility results 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 for, 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 (Fig. 4B & Table 2). Because it is believed that WMH may be a neurological substrate that is 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.

3.3. Associations between WMH and AD (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.

4. Discussion

The goals of this study were 3-fold: to determine the regional localization of WMH with age; to determine the effect of WMH on
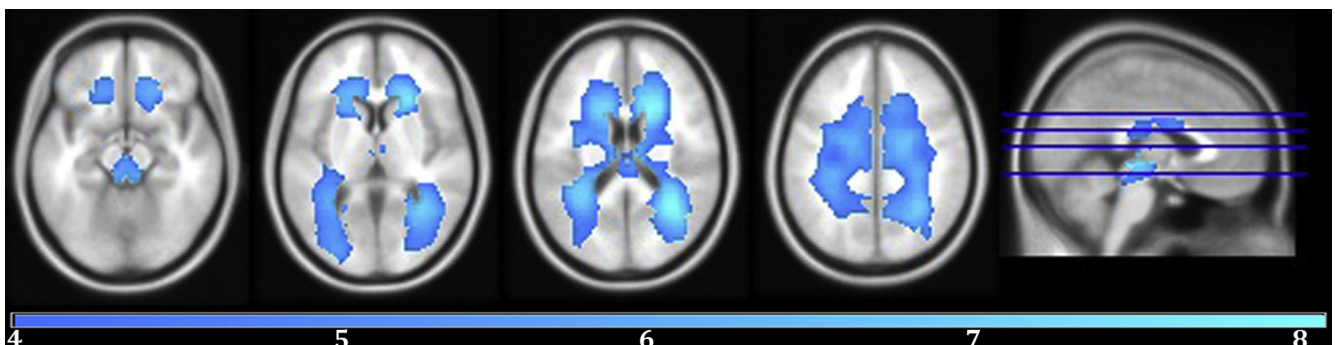

Fig. 2. Areas of positive correlation with age on smoothed white matter hyperintensities (WMH) probability belief maps controlling for intracranial volume and sex are displayed in cool colors (blue). The color bar indicates the t value. Family-wise error (FWE)-correction, $p < 0.05$. Peak voxel coordinates,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

Table 2
Peak voxel MNI coordinates (x, y, z), *t* statistic and *p*-value, and cluster size (k) for each voxel-wise analysis for each significant cluster

Brain region	x	y	z	k	t	p
WMH increase with age (Fig. 2)						
R posterior thalamic radiation	33	−54	19	71,551	8.13	<0.0001
WMH increase with lower Speed and Flexibility factor score (Fig. 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 (Fig. 4B)						
L superior corona radiata	−27	5	34	1838	4.97	<0.0001
R superior corona radiata	28	17	28	726	4.87	<0.0001

Key: L, left; R, right; WMH, white matter hyperintensity.

cognitive function in the context of aging; and to assess the effect of AD risk on WMH in a large sample of healthy late–middle-aged participants. We observed that increasing age and lower cognitive speed and flexibility scores are strongly associated with WMH throughout the 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, in which 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. AD 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 et al., 2000; Soderlund 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 that of our sample, Raz et al. found a relationship between frontal WMH, including periventricular regions, and executive function (Raz et al., 2003). Other studies have found impacts on executive
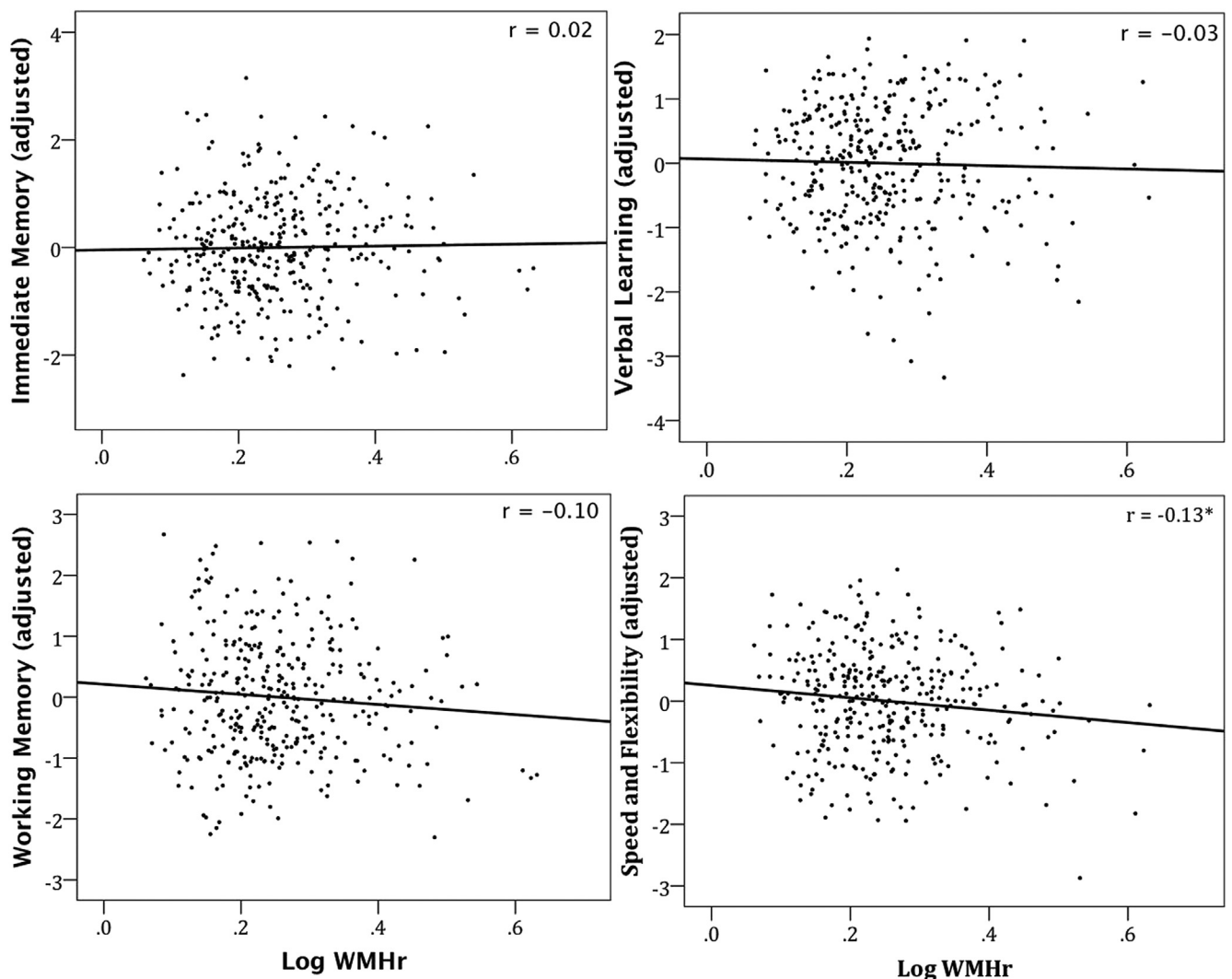

Fig. 3. Residuals of white matter hyperintensity ratio (WMHr) after adjusting for age, sex, and years of education graphed as a function of cognitive factor scores. * Significant at *p* < 0.05. Abbreviation: WMHr, white matter hyperintensity ratio.
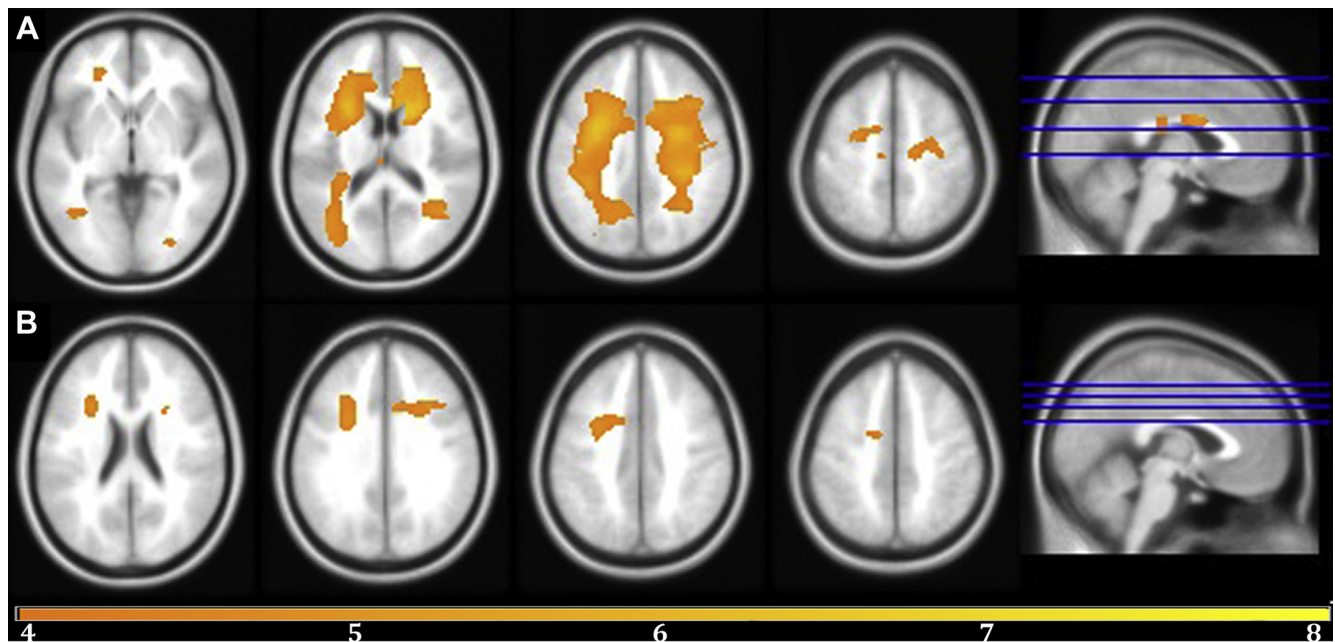
Fig. 4. (A) Areas of negative correlation with Speed and Flexibility factor score controlling for sex, intracranial volume (ICV), and years of education are shown in warm colors (yellow-orange). (B) Areas of negative correlation with Speed and Flexibility factor score controlling for age, sex, years of education, and intracavitary volume (ICV). Family-wise error (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. Abbreviation: FWE, family-wise error.

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 contributed to impairments in executive function regardless of lesion location (Tullberg 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 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 (Carmichael et al., 2012; Gunning-Dixon and Raz, 2000; Smith et al., 2011; Van Petten et al., 2004), and indeed, WMH have been found to underlie episodic memory deficits, even in the absence of hippocampal atrophy (Nordahl et al., 2005). The present 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 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 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 44–48 years, and found that temporal WMH were associated with memory; however in this case the task was nonverbal (face recognition) and only present in men (Bunce et al., 2010). In a primarily male population studied in the Secondary Manifestations of Arterial Disease-Magnetic Resonance Study, WMH burden interacted with brain volume

measures to produce lower executive function, but did not have an effect on memory function (Muller et al., 2011). Likewise, in a study which assessed the contribution of childhood IQ on later-life cognitive function in an older, but nondemented 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 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 with medial temporal lobe based memory tests (Au et al., 2006). A recent study in a cognitively healthy older sample found that memory function was affected by amyloid burden, whereas executive function was more closely associated with WMH (Hedden et al., 2012). Although, episodic memory function can be clearly impacted by WMH burden, at least 1 study suggests that this effect is mediated by executive functioning (Parks et al., 2011). The participants in the present study, albeit— younger, showed an effect of WMH on subcomponents of executive function, which 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 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 a study by Rostrup et al. (2012), which examined an older population. WMH appear to accumulate in periventricular and deep white matter near the precentral gyrus. A voxel-wise study using 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 et al., 2010a, 2010b). 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 (Leunissen et al., 2013; Sasson et al., 2012). A tractography study performed by Leunissen et al. (2013) showed that injury to fibers of the superior corona radiata, which connect the basil ganglia and thalamus to superior frontal gyrus and supplementary motor area, contributes to deficits in task switching. The researchers point to an emerging body of evidence that cortico-subcortical damage may cause executive dysfunction through a lack of cognitive control. The results of the present study, which found that WMH probability in the superior corona radiata was associated with speed and flexibility independently of age (Fig. 4B), provide 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 (Biffi et al., 2010; Debette et al., 2009). In studies that have found a relationship between APOE4 and WMH, the participants were older than the samples in the present study (de Leeuw et al., 2004; Lunetta 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 et al., 2005; Persson et al., 2006; Ryan et al., 2011; Smith et al., 2010).

This study has a few limitations that should be noted. The study is cross-sectional and longitudinal studies are needed to understand the temporal relationship between cognitive performance and the development of WMH (Wardlaw 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. Furthermore, it is important to note that although WMH accounts for some of the effects on cognitive function (Soderlund et al., 2003; Vannorsdall et al., 2009), other aspects of neural health are important, as are the myriad lifestyle and genetic factors that affect neural health and cognition. Finally, given the heterogenous nature of WMH in aging, larger studies, different samples or different methods of assessing WMH could produce different results.

In 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 on age-related cognitive decline.

Disclosure statement

The authors have no actual or potential conflicts of interest.

Acknowledgements

References

Aggarwal, N.T., Wilson, R.S., Bienias, J.L., De Jager, P.L., Bennett, D.A., Evans, D.A., DeCarli, C., 2010. The association of magnetic resonance imaging measures with cognitive function in a biracial population sample. Arch. Neurol. 67, 475—482.

Alves, G.S., O'Dwyer, L., Jurcoane, A., Oertel-Knochel, V., Knochel, C., Prvulovic, D., Sudo, F., Alves, C.E., Valente, L., Moreira, D., Fubetaer, F., Karakaya, T., Pantel, J., Engelhardt, E., Laks, J., 2012. Different patterns of white matter degeneration using multiple diffusion indices and volumetric data in mild cognitive impairment and Alzheimer patients. PLoS One 7, e52859.

Au, R., Massaro, J.M., Wolf, P.A., Young, M.E., Beiser, A., Seshadri, S., D'Agostino, R.B., DeCarli, C., 2006. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study. Arch. Neurol. 63, 246—250.

Basile, A.M., Pantoni, L., Pracucci, G., Asplund, K., Chabriat, H., Erkinjuntti, T., Fazekas, F., Ferro, J.M., Hennerici, M., O'Brien, J., Scheltens, P., Visser, M.C., Wahlund, L.O., Waldemar, G., Wallin, A., Inzitari, D., 2006. Age, hypertension, and lacunar stroke are the major determinants of the severity of age-related white matter changes. The LADIS (Leukoaraiosis and Disability in the Elderly) Study. Cerebrovasc. Dis. 21, 315—322.

Bendlin, B.B., Fitzgerald, M.E., Ries, M.L., Xu, G., Kastman, E.K., Thiel, B.W., Rowley, H.A., Lazar, M., Alexander, A.L., Johnson, S.C., 2010a. White matter in aging and cognition: a cross-sectional study of microstructure in adults aged eighteen to eighty-three. Dev. Neuropsychol. 35, 257—277.

Bendlin, B.B., Ries, M.L., Canu, E., Sodhi, A., Lazar, M., Alexander, A.L., Carlsson, C.M., Sager, M.A., Asthana, S., Johnson, S.C., 2010b. White matter is altered with parental family history of Alzheimer's disease. Alzheimers Dement. 6, 394—403.

Biffi, A., Anderson, C.D., Desikan, R.S., Sabuncu, M., Cortellini, L., Schmansky, N., Salat, D., Rosand, J., 2010. Genetic variation and neuroimaging measures in Alzheimer disease. Arch. Neurol. 67, 677—685.

Brickman, A.M., Provenzano, F.A., Muraskin, J., Manly, J.J., Blum, S., Apa, Z., Stern, Y., Brown, T.R., Luchsinger, J.A., Mayeux, R., 2012. Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. Arch. Neurol. 69, 1621—1627.

Brickman, A.M., Siedlecki, K.L., Muraskin, J., Manly, J.J., Luchsinger, J.A., Yeung, L.K., Brown, T.R., DeCarli, C., Stern, Y., 2011. White matter hyperintensities and cognition: testing the reserve hypothesis. Neurobiol. Aging 32, 1588—1598.

Bunce, D., Anstey, K.J., Cherbuin, N., Burns, R., Christensen, H., Wen, W., Sachdev, P.S., 2010. Cognitive deficits are associated with frontal and temporal lobe white matter lesions in middle-aged adults living in the community. PloS one 5, e13567.

Carmichael, O., Mungas, D., Beckett, L., Harvey, D., Tomaszewski Farias, S., Reed, B., Olichney, J., Miller, J., Decarli, C., 2012. MRI predictors of cognitive change in a diverse and carefully characterized elderly population. Neurobiol. Aging 33, 83—95.

Cuenco, K.T., Green, R.C., Zhang, J., Lunetta, K., Erlich, P.M., Cupples, L.A., Farrer, L.A., DeCarli, C., 2008. Magnetic resonance imaging traits in siblings discordant for Alzheimer disease. J. Neuroimaging. 18, 268—275.

de Groot, J.C., de Leeuw, F.E., Oudkerk, M., van Gijn, J., Hofman, A., Jolles, J., Breteler, M.M., 2000. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann. Neurol. 47, 145—151.

de leeuw, F.E., de Groot, J.C., Achten, E., Oudkerk, M., Ramos, L.M., Heijboer, R., Hofman, A., Jolles, J., van Gijn, J., Breteler, M.M., 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J. Neurol. Neurosurg. Psychiatry 70, 9—14.

de Leeuw, F.E., Richard, F., de Groot, J.C., van Duijn, C.M., Hofman, A., Van Gijn, J., Breteler, M.M., 2004. Interaction between hypertension, apoE, and cerebral white matter lesions. Stroke 35, 1057—1060.

Debette, S., Markus, H.S., 2010. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 341, c3666.

Debette, S., Wolf, P.A., Beiser, A., Au, R., Himali, J.J., Pikula, A., Auerbach, S., Decarli, C., Seshadri, S., 2009. Association of parental dementia with cognitive and brain MRI measures in middle-aged adults. Neurology 73, 2071—2078.

Dowling, N.M., Hermann, B., La Rue, A., Sager, M.A., 2010. Latent structure and factorial invariance of a neuropsychological test battery for the study of preclinical Alzheimer's disease. Neuropsychology 24, 742—756.

Ferro, J.M., Madureira, S., 2002. Age-related white matter changes and cognitive impairment. J. Neurol. Sci. 203-204, 221—225.

Frisoni, G.B., Galluzzi, S., Pantoni, L., Filippi, M., 2007. The effect of white matter lesions on cognition in the elderly–small but detectable. Nat. Clin. Pract. Neurol. 3, 620–627.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14 (1 Pt 1), 21–36.

Grimmer, T., Faust, M., Auer, F., Alexopoulos, P., Forstl, H., Henriksen, G., Perneczky, R., Sorg, C., Yousefi, B.H., Drzezga, A., Kurz, A., 2012. White matter hyperintensities predict amyloid increase in Alzheimer's disease. Neurobiol. Aging 33, 2766–2773.

Gunning-Dixon, F.M., Raz, N., 2000. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology 14, 224–232.

Gunning-Dixon, F.M., Raz, N., 2003. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. Neuropsychologia 41, 1929–1941.

Guzman, V.A., Carmichael, O.T., Schwarz, C., Tosto, G., Zimmerman, M.E., Brickman, A.M., 2013. White matter hyperintensities and amyloid are independently associated with entorhinal cortex volume among individuals with mild cognitive impairment. Alzheimers Dement 9, S124–S131.

Hedden, T., Mormino, E.C., Amariglio, R.E., Younger, A.P., Schultz, A.P., Becker, J.A., Buckner, R.L., Johnson, K.A., Sperling, R.A., Rentz, D.M., 2012. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. J. Neurosci. 32, 16233–16242.

Keihaninejad, S., Heckemann, R.A., Fagiolo, G., Symms, M.R., Hajnal, J.V., Hammers, A., 2010. A robust method to estimate the intracranial volume across MRI field strengths (1.5T and 3T). NeuroImage 50, 1427–1437.

Leunissen, I., Coxon, J.P., Caeyenberghs, K., Michiels, K., Sunaert, S., Swinnen, S.P., 2013. Task switching in traumatic brain injury relates to cortico-subcortical integrity. Hum. Brain Mapp.

Li, S., Pu, F., Shi, F., Xie, S., Wang, Y., Jiang, T., 2008. Regional white matter decreases in Alzheimer's disease using optimized voxel-based morphometry. Acta Radiol. 49, 84–90.

Lunetta, K.L., Erlich, P.M., Cuenco, K.T., Cupples, L.A., Green, R.C., Farrer, L.A., Decarli, C., 2007. Heritability of magnetic resonance imaging (MRI) traits in Alzheimer disease cases and their siblings in the MIRAGE study. Alzheimer Dis. Assoc Disord. 21, 85–91.

Maillard, P., Carmichael, O., Fletcher, E., Reed, B., Mungas, D., DeCarli, C., 2012. Coevolution of white matter hyperintensities and cognition in the elderly. Neurology 79, 442–448.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34, 939–944.

Muller, M., Appelman, A.P., van der Graaf, Y., Vincken, K.L., Mali, W.P., Geerlings, M.I., 2011. Brain atrophy and cognition: interaction with cerebrovascular pathology? Neurobiol. Aging 32, 885–893.

Murray, M.E., Senjem, M.L., Petersen, R.C., Hollman, J.H., Preboske, G.M., Weigand, S.D., Knopman, D.S., Ferman, T.J., Dickson, D.W., Jack Jr., C.R., 2010. Functional impact of white matter hyperintensities in cognitively normal elderly subjects. Arch. Neurol. 67, 1379–1385.

Nierenberg, J., Pomara, N., Hoptman, M.J., Sidtis, J.J., Ardekani, B.A., Lim, K.O., 2005. Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers. Neuroreport 16, 1369–1372.

Nordahl, C.W., Ranganath, C., Yonelinas, A.P., DeCarli, C., Reed, B.R., Jagust, W.J., 2005. Different mechanisms of episodic memory failure in mild cognitive impairment. Neuropsychologia 43, 1688–1697.

Parks, C.M., Iosif, A.M., Farias, S., Reed, B., Mungas, D., DeCarli, C., 2011. Executive function mediates effects of white matter hyperintensities on episodic memory. Neuropsychologia 49, 2817–2824.

Persson, J., Lind, J., Larsson, A., Ingvar, M., Cruts, M., Van Broeckhoven, C., Adolfsson, R., Nilsson, L.G., Nyberg, L., 2006. Altered brain white matter integrity in healthy carriers of the APOE epsilon4 allele: a risk for AD? Neurology 66, 1029–1033.

Raz, N., Rodrigue, K.M., Acker, J.D., 2003. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. Behav. Neurosci. 117, 1169–1180.

Reitan, R.M., Wolfson, D., 1993. The Halstead-reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press, Tucson, AZ.

Rostrup, E., Gouw, A.A., Vrenken, H., van Straaten, E.C., Ropele, S., Pantoni, L., Inzitari, D., Barkhof, F., Waldemar, G., 2012. The spatial distribution of age-related white matter changes as a function of vascular risk factors–results from the LADIS study. NeuroImage 60, 1597–1607.

Ryan, L., Walther, K., Bendlin, B.B., Lue, L.F., Walker, D.G., Glisky, E.L., 2011. Age-related differences in white matter integrity and cognitive function are related to APOE status. NeuroImage 54, 1565–1577.

Sager, M.A., Hermann, B., La Rue, A., 2005. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. J. Geriatr. Psychiatry Neurol. 18, 245–249.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103, 403–428.

Sasson, E., Doniger, G.M., Pasternak, O., Tarrasch, R., Assaf, Y., 2012. Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. Brain Struct. Funct. 217, 503–515.

Schmidt, P., Gaser, C., Arsic, M., Buck, D., Forschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V.J., Zimmer, C., Hemmer, B., Muhlau, M., 2012. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. NeuroImage 59, 3774–3783.

Smith, C.D., Chebrolu, H., Andersen, A.H., Powell, D.A., Lovell, M.A., Xiong, S., Gold, B.T., 2010. White matter diffusion alterations in normal women at risk of Alzheimer's disease. Neurobiol. Aging 31, 1122–1131.

Smith, E.E., Salat, D.H., Jeng, J., McCreary, C.R., Fischl, B., Schmahmann, J.D., Dickerson, B.C., Viswanathan, A., Albert, M.S., Blacker, D., Greenberg, S.M., 2011. Correlations between MRI white matter lesion location and executive function and episodic memory. Neurology 76, 1492–1499.

Soderlund, H., Nilsson, L.G., Berger, K., Breteler, M.M., Dufouil, C., Fuhrer, R., Giampaoli, S., Hofman, A., Pajak, A., de Ridder, M., Sans, S., Schmidt, R., Launer, L.J., 2006. Cerebral changes on MRI and cognitive function: the CASCADE study. Neurobiol. Aging 27, 16–23.

Soderlund, H., Nyberg, L., Adolfsson, R., Nilsson, L.G., Launer, L.J., 2003. High prevalence of white matter hyperintensities in normal aging: relation to blood pressure and cognition. Cortex 39, 1093–1105.

Spreen, O., Strauss, E., 1998. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, New York.

Trenerry, M.R., 1989. Stroop Neuropsychological Screening Test Manual. Psychological Assessment Resources, Adessa, FL.

Tullberg, M., Fletcher, E., DeCarli, C., Mungas, D., Reed, B.R., Harvey, D.J., Weiner, M.W., Chui, H.C., Jagust, W.J., 2004. White matter lesions impair frontal lobe function regardless of their location. Neurology 63, 246–253.

Valdes Hernandez, M.D., Booth, T., Murray, C., Gow, A.J., Penke, L., Morris, Z., Maniega, S.M., Royle, N.A., Aribisala, B.S., Bastin, M.E., Starr, J.M., Deary, I.J., Wardlaw, J.M., 2013. Brain white matter damage in aging and cognitive ability in youth and older age. Neurobiol Aging 34, 2740–2747.

Van Petten, C., Plante, E., Davidson, P.S., Kuo, T.Y., Bajuscak, L., Glisky, E.L., 2004. Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. Neuropsychologia 42, 1313–1335.

Vannorsdall, T.D., Waldstein, S.R., Kraut, M., Pearlson, G.D., Schretlen, D.J., 2009. White matter abnormalities and cognition in a community sample. Arch. Clin. Neuropsychol. 24, 209–217.

Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., Black, S.E., Brayne, C., Breteler, M., Chabriat, H., Decarli, C., de Leeuw, F.E., Doubal, F., Duering, M., Fox, N.C., Greenberg, S., Hachinski, V., Kilimann, I., Mok, V., Oostenbrugge, R., Pantoni, L., Speck, O., Stephan, B.C., Teipel, S., Viswanathan, A., Werring, D., Chen, C., Smith, C., van Buchem, M., Norrving, B., Gorelick, P.B., Dichgans, M., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 12, 822–838.

Wechsler, D., 1997. WAIS-III: WAIS Adult Intelligence Scale. Psychological Corporation.

Wen, W., Sachdev, P., 2004. The topography of white matter hyperintensities on brain MRI in healthy 60- to 64-year-old individuals. Neuroimage 22, 144–154.

Wen, W., Sachdev, P.S., Li, J.J., Chen, X., Anstey, K.J., 2009. White matter hyperintensities in the forties: their prevalence and topography in an epidemiological sample aged 44-48. Hum. Brain Mapp. 30, 1155–1167.

Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D.M., Reed, B.R., DeCarli, C.S., 2006. Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. Neurology 67, 2192–2198.