

White Matter Predictors of Cognitive Functioning in Older Adults

Irene B. Meier,¹ Jennifer J. Manly,^{1,2,3} Frank A. Provenzano,¹ Karmen S. Louie,¹ Ben T. Wasserman,¹ Erica Y. Griffith,¹ Josina T. Hector,¹ Elizabeth Allocco,¹ AND Adam M. Brickman^{1,2,3}

¹Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, New York

²Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, New York

³Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York

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Abstract

Few studies have applied multiple imaging modalities to examine cognitive correlates of white matter. We examined the utility of T2-weighted magnetic resonance imaging (MRI)-derived white matter hyperintensities (WMH) and diffusion tensor imaging-derived fractional anisotropy (FA) to predict cognitive functioning among older adults. Quantitative MRI and neuropsychological evaluations were performed in 112 older participants from an ongoing study of the genetics of Alzheimer's disease (AD) in African Americans. Regional WMH volumes and FA were measured in multiple regions of interest. We examined the association of regional WMH and an FA summary score with cognitive test performance. Differences in WMH and FA were compared across diagnostic groups (i.e., normal controls, mild cognitive impairment, and probable AD). Increased WMH volume in frontal lobes was associated with poorer delayed memory performance. FA did not emerge as a significant predictor of cognition. White matter hyperintensity volume in the frontal and parietal lobes was increased in MCI participants and more so in AD patients relative to controls. These results highlight the importance of regionally distributed small vessel cerebrovascular disease in memory performance and AD among African American older adults. White matter microstructural changes, quantified with diffusion tensor imaging, appear to play a lesser role in our sample. (*JINS*, 2012, *18*, 414–427)

Keywords: Magnetic resonance imaging, White matter hyperintensities, Diffusion tensor imaging, Cognition, Alzheimer's disease, African Americans

INTRODUCTION

In recent years, advances in acquisition and analysis of high resolution magnetic resonance imaging (MRI) data have allowed for the precise and reliable visualization and quantification of normal and abnormal cerebral white matter. Two important MRI sequences that can be used to quantify white matter include diffusion tensor imaging (DTI), and T2-weighted imaging. Both imaging modalities have been used in the context of cognitive aging and dementia research, but few studies have considered them simultaneously.

Diffusion tensor imaging provides clues about white matter microstructure by exploiting the differential diffusion of water across tissue types (Mori & Barker, 1999; Pierpaoli &

Basser, 1996). Because fractional anisotropy (FA), the most common DTI metric, reflects water molecule coherence, it can be used to estimate the orientation and integrity of fiber bundles (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Mori & Barker, 1999; Mori, Crain, Chacko, & van Zijl, 1999). Decreased FA has been shown to be related to poorer performance across several cognitive domains in healthy older individuals (Madden, Bennett, & Song, 2009; Penke & Deary, 2010; Vernooij et al., 2009) and across the adult lifespan (Grieve, Williams, Paul, Clark, & Gordon, 2007), but the exact mechanisms linking cognitive functioning with white matter microstructural integrity are not fully understood. Lowered FA could result from localized microstructural processes that affect single tracts in some individuals, but it could also be to some extent a global phenomenon that affects many tracts simultaneously (Wahl et al., 2010).

Diffusion tensor imaging has also been used to examine white matter microstructural changes associated with neurodegenerative conditions, such as Alzheimer's disease (AD).

Correspondence and reprint requests to: Adam M. Brickman, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, P&S Box 16, New York, NY 10032. E-mail: amb2139@columbia.edu

Measures of white matter integrity have been reported to be lower among patients with AD relative to controls in several regions throughout the brain (Bozzali et al., 2002; Damoiseaux et al., 2009; Huang & Auchs, 2007; Medina et al., 2006; Naggara et al., 2006; Takahashi et al., 2002; Xie et al., 2006), and to correlate with the degree of cognitive impairment (Bozzali et al., 2002; Duan et al., 2006). Despite observations of FA reduction among patients with AD, findings regarding the regional specificity of these observations have been less consistent. As variance in white matter integrity estimated with FA is highly collinear across tracts, some authors have suggested deriving summary measures of total white matter integrity to maximize the reliability of these measures (Penke et al., 2010). In the current study, we derive a general white matter integrity summary factor as the primary DTI measure of interest.

Whereas DTI can be used to estimate variability in the integrity of white matter due to aging, disease, or inter-individual variability, white matter hyperintensities (WMH) are a reflection of frank macrostructural white matter pathology. White matter hyperintensities most likely reflect small vessel cerebrovascular disease, as shown in pathological studies (Fazekas et al., 1993; Gouw et al., 2011; C.D. Smith, Snowdon, Wang, & Markesbery, 2000), and suggested by their strong associations with vascular risk factors, such as high or fluctuating blood pressure, diabetes, and heart disease (Brickman et al., 2010; Brickman, Schupf, et al., 2008; DeCarli et al., 1999; Liao et al., 1996, 1997; Manolio et al., 1994; Meyer et al., 1999; Raz, Rodrigue, Kennedy, & Acker, 2007; Strassburger et al., 1997; Viswanathan, Rocca, & Tzourio, 2009). They are more prevalent and severe among patients with AD than controls (Barber et al., 1999; Capizzano et al., 2004; Scheltens et al., 1992; Tanabe et al., 1997) and have been shown to be associated with a precipitous cognitive decline among patients with prevalent AD (Brickman, Honig, et al., 2008; Burns et al., 2005; Yoshita et al., 2006). Individuals at greatest risk for the development of AD have increased WMH volume relative to those at lesser risk (Luchsinger et al., 2009). White matter hyperintensities are distributed disproportionately in frontal (Capizzano et al., 2004) and parietal regions (Gootjes et al., 2004), and while generally emerging as homogenous signal on MRI, the regional distribution might point to distinct underlying pathological features that might play a unique role in AD (Brickman, Muraskin, & Zimmerman, 2009).

While most previous studies have examined the relation of either WMH or FA with cognition or AD, few have examined whether one is a better predictor of cognitive function among older adults than the other in the same sample. Our overall aim was to examine the role of white matter microstructure variability (estimated with DTI) and markers of white matter pathology (appreciated through examination of WMH) in cognitive aging and dementia. First, we were interested in examining the association between FA and WMH to determine to what extent the two measures reflect the same process. Next, we examined the utility of regional WMH and DTI-derived FA to predict cognitive functioning among older

adults; we were interested in testing whether FA and WMH were independently related to specific cognitive functions, or whether one marker of white matter was a better predictor of cognitive function than the other one. Finally, we compared WMH volume and DTI-derived FA across three diagnostic categories (i.e., normal control, mild cognitive impairment [MCI], and AD) that were determined independently of imaging findings. Based on findings from the extant literature (Brickman et al., 2009; Luchsinger et al., 2009; Smith et al., 2008), we expected higher WMH burden to be associated with a more severe degree of cognitive impairment and vary as a function of diagnostic groups. Specifically, although WMH burden is often linked to executive dysfunction (Gunning-Dixon & Raz, 2000), an emerging literature suggests a role of WMH in the pathogenesis of AD, a neurodegenerative condition marked primarily by memory impairment. Thus, we hypothesized that there would be an association between WMH and the AD “phenotype” as a quantitative trait (i.e., memory function as a continuous measure) or as a diagnostic entity. Similarly, we expected lower FA to be associated with poorer cognitive functioning, either defined continuously or as diagnostic entity. As FA and WMH ostensibly reflect distinct aspects of white matter (i.e., micro- and macrostructure), we hypothesized that each to be independently associated with cognition.

This imaging substudy is part of a larger effort that seeks to elucidate unique genes involved with AD pathogenesis among African Americans. Increased incidence and prevalence rates of AD and cognitive dysfunction among African Americans have been reported in the literature (Gurland et al., 1999; Perkins & Schisterman, 2006; M.X. Tang et al., 2001; Unverzagt, Hall, Torke, & Rediger, 1996). Our belief is that one potential source of discrepancies across racial groups in diagnosis could be due to differences in cerebrovascular disease. While we do not include members of different racial groups in the current study for explicit comparison, African Americans have been severely under-represented in most large-scale neuroimaging studies of cognitive aging and dementia and we believe that it is important to establish brain-behavior relationships in this group.

METHODS

The parent study is a multi-site effort that includes the participation of investigators at Columbia University, Duke University, North Carolina A&T State University, Vanderbilt University, and University of Miami. A subset of participants at the Columbia University site was recruited for participation in an MRI sub-study. The current report focuses on these individuals. This study was approved by an Institutional Review Board at Columbia University Medical Center.

Subjects

Inclusion criteria for the parent study included age greater than 50 years; self-identification as Black or African American

and non-Hispanic; and fluent in English. Participants in the MRI sub-study gave written informed consent for MRI scanning and did not have contraindications.

Neuropsychological Evaluation

Participants were administered a neuropsychological battery, which included representative tests from several cognitive domains. The battery comprised the following tests: Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975); Digit Symbol subtest of the Wechsler Adult Intelligence Scale - Revised (Wechsler, 1997); Trailmaking Test Parts A and B (Reitan, 1978); Digit Span Forward and Backward (Wechsler, 1997); California Verbal Learning Test-2 (CVLT-II; Trials 1–5 free recall, short delayed free recall, long delayed free recall, recognition hits-false positives) (Delis, Kramer, Kaplan, & Ober, 2000); Logical Memory Test (immediate recall, delayed recall) (Wechsler, 1997); Rey-Osterrieth Complex Figure Test (immediate recall, delayed recall) (Osterrieth, 1944); Controlled Oral Word Association Test (CFL; (Benton & Hamsher, 1976)); Category Fluency Test (animal and vegetable naming; (Goodglass, 1983; Morris et al., 1989); and 30-item Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983; Weintraub et al., 2009). All neuropsychological data were analyzed in raw form.

Participants underwent a diagnostic work-up, including a medical history, assessment of functional status and memory complaints, and a neurological exam. Informants were interviewed whenever available and asked about functional status (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), neuropsychiatric symptoms (Cummings, Mega, Gray, Rosenberg-Thompson, & Carusi, 1994), and symptom onset (Sano, Stern, Mayeux, Hartman, & Devanand, 1987). These data, along with performance on the neuropsychological battery, were reviewed at a diagnostic consensus conference that included at least two attending neuropsychologists with expertise in this area. Neuroimaging data were not considered in the diagnostic formulation. Participants were categorized as normal controls, mild cognitive impairment (MCI) (Petersen et al., 1999), or as meeting criteria for dementia (American Psychiatric, 1994). Probable AD was diagnosed following established research criteria (McKhann et al., 1984). Some participants had evidence of some cognitive impairment which the diagnosticians did not believe that they met MCI criteria, but rather that the pattern of cognitive performance reflected lifelong functioning. For these participants, a diagnosis of “cognitive impairment not MCI” was assigned.

Participants were asked whether they had ever been diagnosed with or whether they were currently being treated for hypertension, diabetes mellitus, myocardial infarction, congestive heart failure, any other heart disease, and/or stroke. These dichotomous variables were summed to create a single peripheral vascular disease summary score, similar to what we have done in previous studies (Brickman, Schupf, et al., 2008).

Neuroimaging

Magnetic resonance imaging (MRI) was acquired with a 1.5 Tesla Philips Intera scanner at Columbia University. The following images were acquired in the axial orientation: high-resolution three-dimensional (3D) T1-weighted anatomical (echo time/repetition time [TE/TR]: 2.1/20, field of view [FOV]: 240, Matrix: 256 × 256, flip angle: 20°, slice thickness: 1.3 mm, slices: 105), fluid attenuated inverse recovery (FLAIR) T2-weighted (TE/TR: 5500/144, IR: 1900, FOV: 250, Matrix: 192 × 256, slice thickness: 3 mm, slices: 47 no gap), 16-direction DTI (TR/TE: 10624, FOV: 224, Matrix: 112 × 112, slice thickness: 2 mm, slices: 70 no gap). Other MRI sequences were collected as part of the study, including gradient echo and T2-weighted (without fluid attenuation), but were not used in the current analyses.

White Matter Hyperintensity Quantification

White matter hyperintensity volumes were derived on T2-weighted FLAIR images as described previously (Brickman et al., 2009, 2011; Oliveira, Brickman, Provenzano, Mura-skin, & Louis, in press). Briefly, T1-weighted images were segmented into grey matter, white matter, and cerebrospinal fluid tissue classes with SPM. The normalization parameters were applied to the T2-weighted and T1-weighted images to transform them into standardized atlas space. FLAIR images were skull stripped/brain extracted using the segmented tissue classes from the T1-weighted image. On each FLAIR image, WMH seeds were defined as areas that were 2.7 SD or greater above the mean intensity value of the entire image. Once seeds were placed, each one passed through a mean intensity-based region-growing algorithm that used a 10-point connectivity scheme to label adjacent voxels that fell within 5% of the mean intensity value for the seed. The newly labeled voxels were added to the labeled voxels and a new intensity mean was calculated. This process continued iteratively until all hyperintense voxels were labeled. White matter hyperintensity volume was the sum of all labeled voxels multiplied by voxel dimensions. To calculate regional (i.e., frontal, temporal, parietal, and occipital) WMH volumes, an anatomical atlas (Admiraal-Behloul et al., 2004) was spatially normalized with the inverse transform matrix generated from the segmentation of the T1-weighted image to each participant's labeled FLAIR image. Each region within the anatomical atlas was defined by a unique identification parameter and intersection of the labeled WMH with the unique anatomical label defined the regional WMH volume. Figure 1 displays an example of WMH labeling for a single subject.

Diffusion Tensor Imaging

Diffusion tensor imaging data were processed with the fMRI Software Library (FSL 4.1.3. release; www.fmrib.ox.ac.uk/fsl) fMRIB Diffusion Toolbox and tract based spatial statistics (TBSS) (Smith et al., 2004, 2006). Briefly, after individual subjects raw DTI images were aligned to the $b = 0$ image (Jenkinson, Bannister, Brady, & Smith, 2002), a mean FA

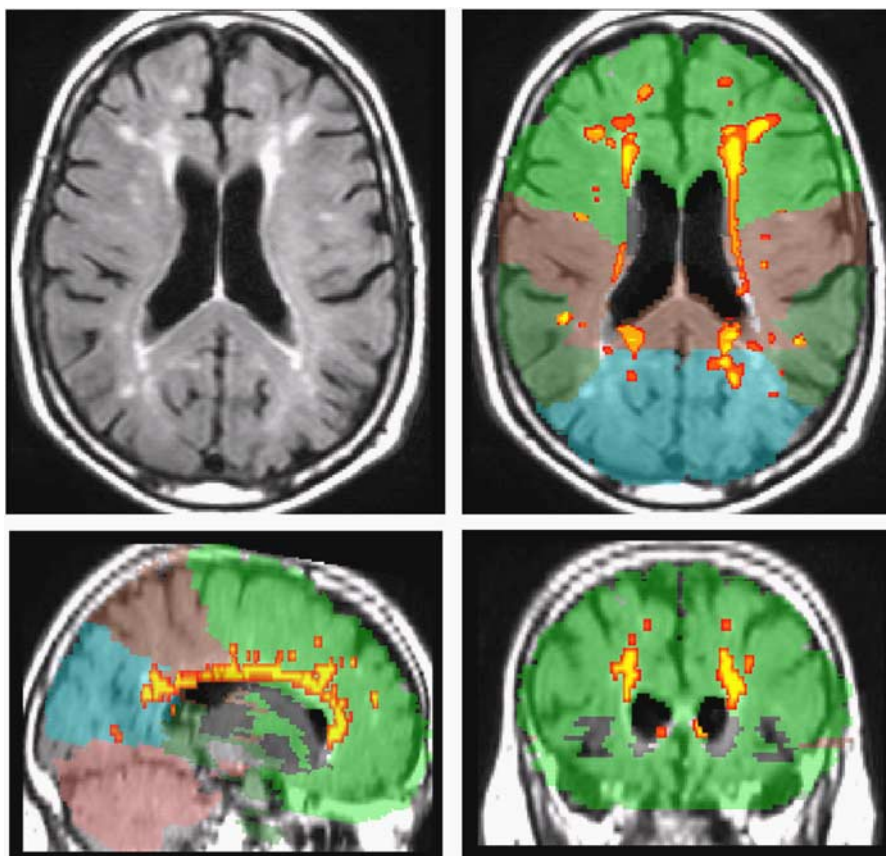


Fig. 1. Example of regional white matter hyperintensities (WMH) quantification for one subject. Left top: raw T2-weighted FLAIR image. Other panels: Orthogonal view of labeled image. White matter hyperintensities are labeled with red/yellow. Colors correspond to cerebral lobes (green: frontal, brown: parietal, dark green: temporal, blue: occipital, mauve: cerebellum).

skeleton was created by thinning the group mean FA image. This skeleton is a representation of the centers of the white matter tracts common to the group. All FA images were then nonlinearly transformed into the space of the mean image. For each subject, local FA maxima were projected onto the group template skeleton (Smith et al., 2006). Next, we used JHU White Matter Label Map included with FSL to identify sections of the white matter skeleton that represent a number of white matter fiber tracts in both brain hemispheres (listed in Figure 2 caption). Average FA values for each white matter tract were calculated from the white matter skeleton and values from the left and right hemispheres were averaged together where applicable. Figure 2 displays the regions of interest superimposed on the skeletonized map.

Given the collinearity among FA measurements in multiple tracts, our interest in global measures of white matter integrity, and the lack of reported regional consistency in the extant literature, we focused on a summary tract measure as a marker of global white matter integrity. Furthermore, a derived summary measure for FA increases the reliability of measurement because it comprises several tracts and helps minimize the number of statistical comparisons. Following procedures put forth by Penke and colleagues (Penke et al., 2010), mean FA values from each ROI were subjected to a

principal component analysis and the first derived factor, which explained 54.9% of the total variance, was used in subsequent analyses. Apart from four tracts, factor loadings were all greater than 0.64. Factor loadings that were less than 0.64 came from pontine crossing-tracts part of the middle cerebellar peduncles, corticospinal tract, inferior cerebellar peduncles, and the tapetum, which ranged in factor loading from 0.284 to 0.482. In *post hoc* exploratory analyses we did, however, also examine individual tracts that have been implicated in AD, including inferior longitudinal fasciculus, uncinate fasciculus, fornix, and genu of the corpus callosum (Kiuchi et al., 2009; Liu et al., 2011; Pievani et al., 2010; Stricker et al., 2009).

Relative Brain Volume

A measure of total relative brain volume was derived with SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Total relative brain volume was the sum of voxels labeled as grey matter and white matter as a ratio to the sum of grey matter, white matter, and cerebrospinal fluid, which were derived using default settings. This measure was used in statistical analyses to control for individual differences in atrophy.

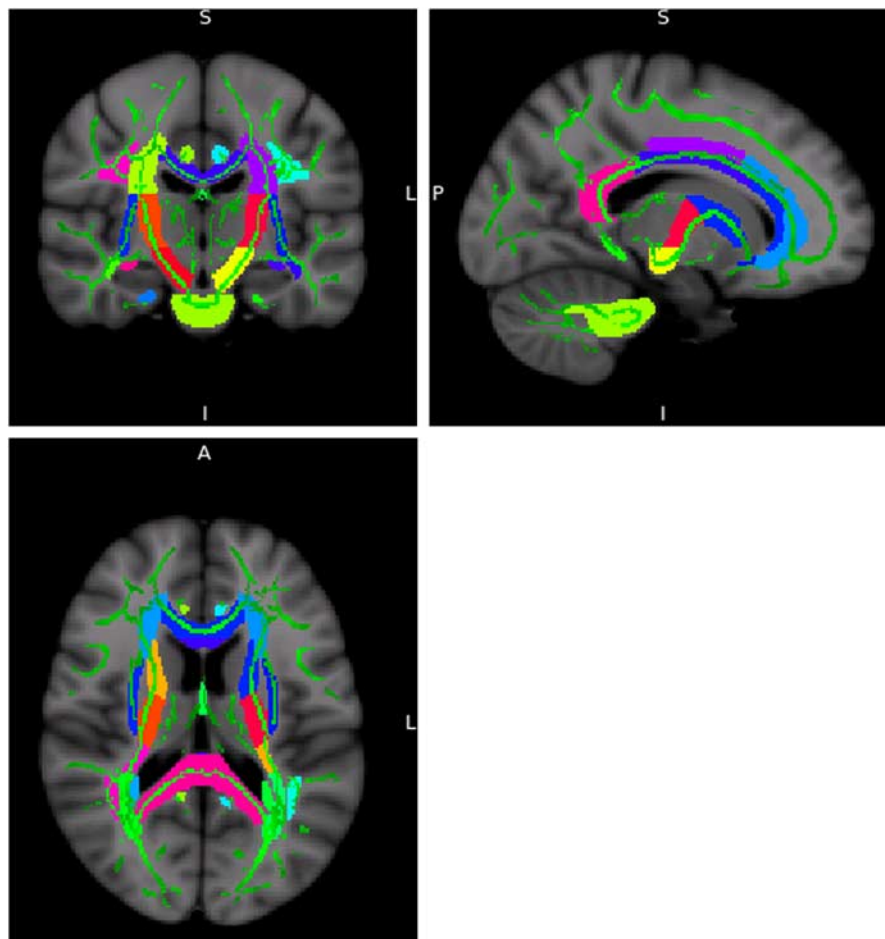


Fig. 2. “Skeletonized” diffusion tensor imaging (DTI) map indicating fractional anisotropy (FA) regions of interest (ROIs; colors) used to derive the summary FA score superimposed onto the mean FA skeleton (green) of the DTI subjects. The summary score comprised the following tracts: middle cerebellar peduncles, pontine crossing tracts part of the middle cerebellar peduncles, genu of the corpus callosum, body of the corpus callosum, splenium of the corpus callosum, fornix column and fornix body, corticospinal tract, medial lemniscus, inferior cerebellar peduncles, superior cerebellar peduncles, cerebral peduncles, anterior limb of the internal capsule, posterior limb of the internal capsule, retrolenticular part of the internal capsule, anterior corona radiata, superior corona radiata, posterior corona radiata, posterior thalamic radiation including optic radiation, sagittal striatum including the inferior longitudinal fasciculus, external capsule, cingulum-cingulate gyrus, cingulum hippocampus, fornix cres stria terminalis, superior longitudinal fasciculus, uncinata fasciculus, and the tapetum.

Statistical analysis

Descriptive demographic data, including age, sex distribution, and number of years of education, were generated for the entire imaging sample and compared across diagnostic subgroups with analysis of variance (ANOVA) and χ^2 tests. Demographic features were also compared between the MRI sub-study participants and the remaining Columbia University site participants who did not participate in the MRI sub-study ($n = 325$, at the time of analysis). Descriptive statistics for the neuroimaging markers and performance on the neuropsychological tests were also generated and compared with ANOVA across groups. For statistical tests to address the study hypotheses, both parametric and non-parametric procedures were used. The relationship between

regional WMH volumes and the FA factor score was examined with bivariate Pearson and Spearman correlations. A series of multiple linear regression analyses was run to examine associations of the white matter variables with the neuropsychological outcomes. By including the white matter measures (i.e., WMH and FA) simultaneously in the multiple regression analyses, we were able to compare explicitly the relative and independent association of each with cognition. For these analyses, all subject subgroups were combined and the lobar WMH volumes and FA measure were entered simultaneously and each of the neuropsychological outcomes was examined as dependent variables in separate analyses. Each regression model controlled for age, years of education, and relative brain volume by entering these factors as additional predictors. For all analyses, non-parametric tests were

used as secondary analyses, as WMH volumes are typically not normally distributed. Given that covariate analyses are not possible with non-parametric statistical procedures, we considered the parametric tests as primary and the non-parametric tests (without covariates) as confirmatory. Although it is often possible to normalize positively skewed distributions by taking the log transformation of the data, in our case there was a large proportion of individuals with zero values for WMH volumes in temporal and occipital lobe, making transformation to normality of distribution impossible. In a *post hoc* exploratory manner, we re-ran the analyses with four fiber tracts previously implicated in AD entered individually or together instead of the FA summary measure.

To examine group differences across controls, those with MCI, and those with AD in regional WMH and global FA we constructed two general linear models. Participants classified as “impaired not MCI” were excluded from these analyses. We chose to exclude these individuals from the group analyses because they did not fit into the pre-defined diagnostic categories. We included them in the individual-differences analyses (described above) because we were interested examining white matter correlates of cognition among older adults in general. For regional WMH analysis, Diagnostic Group (NC, MCI, and AD) was a between-groups factor and Lobe (frontal, temporal, parietal, and occipital) was a within-subjects factor. For FA, we ran a similar analysis with Diagnostic Group as the independent variable and the FA factor score as the dependent variable. This analysis was re-run with the four AD-specific FA fiber tracts instead of the FA summary measure. Both analyses controlled for age, education, and relative brain volume. Non-parametric Kruskal-Wallis tests were used to verify significant group differences.

RESULTS

Subject Characteristics

Table 1 displays demographic data for the entire sample and cognitive subgroups. Impaired not MCI subjects were younger than all other groups, normal controls and MCI subjects were similar in age, and patients with AD were older than all other groups (significant main effect of Diagnostic Group, $F(3,108) = 7.724; p < .001$). The groups were similar in sex distribution ($\chi^2(3) = 0.457; p = .928$) and vascular disease histories ($F(3,99) = 0.848; p = .471$). Patients with AD and MCI had fewer years of education than controls, whereas Impaired not MCI, MCI, and AD participants had similar number of years of education (significant main effect of Diagnostic Group, $F(3,106) = 4.865; p < .001$). As expected, AD patients had lower Mini-Mental State Examination (MMSE) scores than MCI participants, who in turn, had lower MMSE than controls. Impaired not MCI subjects and controls had similar MMSE scores (main effect of Diagnostic Group $F(3,105) = 10.17; p < .001$).

In terms of representativeness of the MRI sample in the Columbia site sample, t-tests showed no differences for

Table 1. Subject demographic data

	NC	MCI	AD	Cognitively impaired, not MCI	Total sample	Pairwise comparison ($p < .05$)
N	61	30	9	12	112	
Age, mean yr (SD)	70.87 (6.65)	72.97 (7.87)	81.00 (8.37)	65.67 (9.87)	71.69 (8.60)	Impaired not MCI < (NC = MCI) < AD
Sex, n (% women)	49 (80)	25 (83)	8 (89)	10 (83)	92 (82)	NC = MCI = AD = Impaired not MCI
Education, mean yr (SD)	14.77 (2.62)	12.83 (2.74)	12.38 (1.30)	13.67 (2.64)	13.95 (2.73)	(MCI = AD = Impaired not MCI), (Impaired not MCI = NC)
Vascular summary score mean (SD)	1.00 (0.94)	1.26 (0.94)	0.800 (0.83)	0.833 (0.83)	1.04 (0.92)	NC = MCI = AD = Impaired not MCI
MMSE, mean (SD)	28.13 (1.83)	26.83 (3.05)	22.71 (4.35)	26.92 (3.00)	27.29 (2.85)	(NC = Impaired not MCI), (Impaired not MCI = MCI) < AD

education ($t(434) = 0.592$; $p = .554$) and MMSE total score ($t(435) = 1.552$; $p = .121$), but subjects receiving MRI scans were slightly older ($t(435) = 3.048$; $p = .002$). χ^2 tests showed no difference for sex of the participants ($\chi^2(1) = 0.181$, $p = 0.671$), but there was a difference in the distribution of diagnostic groups ($\chi^2(3) = 13.403$, $p = .004$). In the imaging sample, there was a greater representation of individuals with AD (8% vs. 5%) and individuals who were classified as Impaired not MCI (10% vs. 2%) and lesser representation of normal controls (54% vs. 63%) compared with the remaining subjects.

Omnibus differences for the morphological measures and neuropsychological variables are reported in Table 2. The groups differed in frontal, temporal, and occipital WMH volume as well as FA and performance across all neuropsychological tests. Note that these comparisons were made for descriptive purposes and did not include relevant covariates necessary for inference.

Of the 112 subjects included in the study, DTI data were available for 89 subjects. Diffusion tensor imaging was not available for subjects either due to scan artifacts or because fatigued subjects requested to discontinue the imaging study before the acquisition of the DTI sequence. Individuals with and without DTI available were similar in terms of age ($t(110) = 0.423$; $p = .673$), education ($t(108) = 1.183$; $p = .239$), sex distribution ($\chi^2(1) = 0.457$; $p = .499$), and distribution of diagnosis ($\chi^2(3) = 1.490$; $p = .685$).

Relationship Between Regional WMH and FA

Lower FA was associated with higher WMH volume in frontal ($r = -0.509$; $p < .001$), temporal ($r = 0.464$; $p < .001$), parietal ($r = -0.509$; $p < .001$), and occipital ($r = -0.275$; $p = .009$) lobes. Results of the non-parametric comparisons yielded similar effect sizes, although FA comparisons with temporal and occipital WMH were reduced to non-significance.

Relationship of Regional WMH and FA With Cognition

Increased WMH volume in the frontal lobes was associated with poorer performance on the CVLT long delayed free recall trial (overall model $F(8,78) = 2.632$; $p = .014$). For illustration, the plot of the association between frontal lobe WMH and CVLT long delayed free recall is displayed in Figure 3. This association remained significant when tested with simple bivariate correlations (Spearman's $r = -0.213$; $p = .022$). When the vascular disease summary score was entered into the regression analysis, the overall model was reduced to non-significance, but the relationship between frontal WMH volume and performance remained of similar magnitude (i.e., standardized beta of -0.423 vs. -0.329). Similarly, increased WMH volume was associated with poorer performance on the CVLT recognition trial (overall model $F(8,78) = 3.889$; $p = .001$), which was also verified with simple bivariate correlations (Spearman's $r = -0.195$; $p = .050$). This association remained statistically significant

when the vascular disease summary score was entered into the regression analysis. Increased WMH volume in the temporal lobes was associated with worse performance on the Trailmaking Test Part A and increased WMH volume in the occipital lobes was associated with better performance on the Trailmaking Test Part A (overall model $F(8,78) = 20.737$; $p < .001$). However, when examining these associations with simple bivariate correlations, neither temporal lobe WMH (Spearman's $r = 0.036$; $p = .717$) nor occipital lobe WMH (Spearman's $r = 0.013$; $p = .895$) was associated with performance on the Trailmaking Test Part A. Increased frontal lobe WMH was associated with poorer performance on the Digit Span forward test, although the overall model was not statistically significant ($F(7,32) = 1.581$; $p = .187$) nor was the bivariate correlation (Spearman's $r = -0.257$; $p = .115$). However, as the Digit Span test was only available for a subset of subjects, the lack of statistical significance may reflect insufficient power. Increased WMH in the temporal lobes was unexpectedly associated with better performance on the Logical Memory delayed trial (overall model $F(8,77) = 4.472$; $p < .001$) but this association was not confirmed with simple bivariate correlations (Spearman's $r = -0.179$; $p = .074$). Similarly, increased WMH in temporal lobes was associated with poorer performance on the Boston Naming Test (overall model $F(8,77) = 4.472$; $p < .001$), this association was not confirmed with simple bivariate correlations (Spearman's $r = -0.101$; $p = .316$). Results from all of the regression analyses are presented in Table 3. The FA summary measure was not associated with cognitive test performance in any of the analyses. When the analyses were re-run with the four AD-specific fiber tracts, none was associated reliably with cognitive test performance either when entered individually or together in a single model. In summary, only the significant relationship between higher WMH burden and lower delayed free memory recall was confirmed by non-parametric statistics.

Differences in Regional WMH and FA Between NC, MCI, and AD

The regional distribution pattern of WMH differed across diagnostic groups (significant Diagnostic Group by Lobe interaction, $F(6,273) = 2.325$; $p = .033$). The pattern of the omnibus interaction (see Figure 4) suggests a "dose response" of increased WMH volume in frontal and parietal lobes among patients with AD, followed by subjects with MCI, and normal controls. Formal *post hoc* analyses were conducted with separate ANOVAs for each lobe separately. For frontal lobes, AD patients had significantly greater WMH volume than controls and subjects with MCI. In all other lobes, WMH volume was statistically similar across groups. The frontal lobe differences were confirmed with non-parametric Kruskal-Wallis Test ($p = .028$ for frontal lobes). The overall model comparing FA among the three diagnostic groups showed a trend toward significance ($F(2,71) = 2.893$; $p = .062$). *Post hoc* examination showed that patients with AD had significantly ($p < .05$) lower FA than controls and

Table 2. Descriptive subject neuroimaging and neuropsychological data

	NC	MCI	AD	Cognitive impaired, not MCI	Total sample	Omnibus statistical test
Relative Brain volume, mean (<i>SD</i>)	0.69 (0.11)	0.68 (0.12)	0.67 (0.13)	0.68 (0.14)	0.69 (0.12)	F(3,110) = 0.13, 0.943
Regional WMH volume (cm ³), mean (<i>SD</i>) [median]						
Frontal	1.06 (1.90) [0.42]	1.29 (1.33) [0.87]	3.38 (3.44) [2.27]	1.96 (2.79) [0.92]	1.40 (2.11) [0.73]	F(3,111) = 3.72, <i>p</i> = .014
Temporal	0.14 (0.33) [0.01]	0.10 (0.24) [0.02]	0.63 (1.22) [0.09]	0.08 (0.09) [0.05]	0.16 (0.42) [0.02]	F(3,111) = 3.99, <i>p</i> = .010
Parietal	0.99 (2.15) [0.21]	1.43 (2.84) [0.15]	3.22 (4.34) [1.07]	0.83 (1.02) [0.19]	1.27 (2.55) [0.20]	F(3,111) = 2.23, <i>p</i> = .089
Occipital	0.09 (0.18) [0.03]	0.04 (0.57) [0.01]	0.31 (0.69) [0.06]	0.12 (0.13) [0.09]	0.10 (0.24) [0.03]	F(3,111) = 2.89, <i>p</i> = .039
FA factor score, mean (<i>SD</i>)	0.16 (0.80)	-0.11 (0.90)	-1.46 (1.24)	0.68 (0.77)	0.00 (1.00)	F(3,88) = 10.23, <i>p</i> < .001
Neuropsychological Test Score, mean (<i>SD</i>)						
CVLT Trials 1–5 Free Recall	47.38 (9.30)	34.70 (6.52)	26.00 (6.27)	39.08 (8.43)	41.58 (10.81)	F(3,101) = 23.42, <i>p</i> < .001
CVLT Short Delayed Free Recall	9.18 (2.85)	4.96 (2.38)	0.86 (10.7)	6.83 (2.25)	7.22 (3.62)	F(3,101) = 30.29, <i>p</i> < .001
CVLT Long Delayed Free Recall	9.91 (2.80)	5.30 (3.37)	0.71 (0.95)	6.92 (2.28)	7.71 (3.94)	F(3,101) = 32.18, <i>p</i> < .001
CVLT Recognition (Hits – False Alarms)	10.63 (3.85)	5.26 (4.65)	-2.43 (6.50)	6.08 (5.23)	7.77 (5.73)	F(3,101) = 23.50, <i>p</i> < .001
Digit Symbol total correct	47.38 (23.44)	30.50 (12.29)	7.00 (2.83)	39.25 (11.59)	36.95 (15.69)	F(3,39) = 9.74, <i>p</i> < .001
Trailmaking Test Part A (sec)	40.63 (11.95)	60.25 (29.21)	102.17 (75.20)	47.00 (17.50)	50.38 (29.31)	F(3,101) = 12.69, <i>p</i> < .001
Trailmaking Test Part B (sec)	105.55 (53.76)	207.81 (76.97)	280.00 (40.00)	157.36 (77.93)	143.92 (80.77)	F(3,88) = 20.33, <i>p</i> < .001
Digit Span Forward	8.60 (2.17)	7.00 (1.82)	6.50 (3.54)	5.75 (1.71)	7.46 (2.18)	F(3,37) = 3.01, <i>p</i> = .043
Digit Span Backward	6.93 (1.94)	4.65 (1.22)	2.50 (0.71)	4.00 (0.82)	5.37 (2.01)	F(3,37) = 9.94, <i>p</i> < .001
Rey Figure Copy	27.30 (4.96)	22.98 (6.38)	14.41 (8.31)	25.63 (7.11)	25.16 (6.63)	F(3,101) = 10.55, <i>p</i> < .001
Rey Figure Immediate Recall	11.17 (5.98)	7.98 (4.04)	2.90 (4.04)	8.18 (4.25)	9.53 (5.57)	F(3,99) = 5.60, <i>p</i> = .001
Rey Figure Delayed Recall	10.66 (5.50)	7.90 (3.92)	2.20 (2.30)	9.00 (4.25)	9.31 (5.23)	F(3,97) = 5.68, <i>p</i> = .001
Verbal Fluency: CFL Total	39.23 (12.57)	28.04 (18.83)	28.67 (12.77)	30.33 (10.76)	34.49 (15.15)	F(3,101) = 4.56, <i>p</i> = .005
Category Fluency: Animal Naming	16.48 (4.06)	12.71 (2.76)	9.86 (3.72)	13.83 (4.61)	14.70 (4.31)	F(3,102) = 10.67, <i>p</i> < .001
Logical Memory Immediate Recall	12.14 (3.13)	9.25 (3.32)	6.40 (3.21)	11.42 (2.15)	10.97 (3.46)	F(3,100) = 9.29, <i>p</i> < .001
Logical Memory Delayed Recall	10.84 (3.48)	7.39 (3.07)	2.40 (2.19)	8.92 (1.68)	9.24 (3.80)	F(3,100) = 15.76, <i>p</i> < .001
Boston Naming Test	48.64 (7.58)	40.39 (8.53)	29.40 (10.92)	42.42 (7.40)	44.66 (9.39)	F(3,100) = 13.68, <i>p</i> < .001

Note. Omnibus effects across the four diagnostic groups are reported. Note that no covariates are included in these statistical analyses.

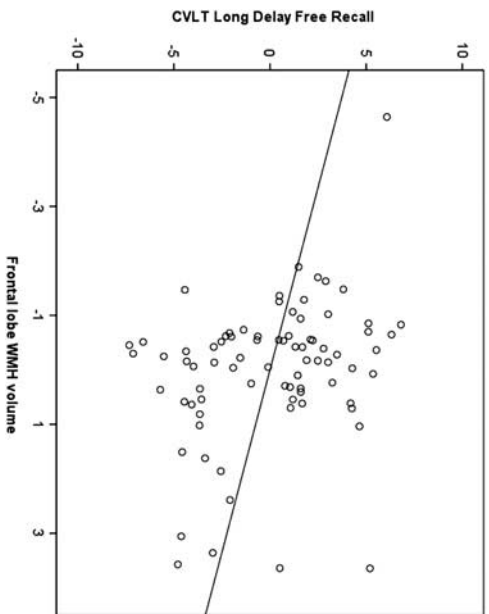


Fig. 3. Scatterplot showing relationship between frontal lobe white matter hyperintensities (WMH) volume and performance on the long delay trial of the California Verbal Learning Test (CVLT). The plot is a partial plot displaying the results from the multiple regression analysis with WMH volumes from the other regions, the FA summary score, relative brain volume, age, and education included as additional covariates. The relationship between frontal lobe WMH volume and performance on the long delay trial of the CVLT remained even after removal of data from the subject who appears in the upper left side of the scatterplot.

subjects with MCI, who were similar to each other. This same pattern emerged for FA in the inferior longitudinal fasciculus and genu of the corpus callosum (i.e., significant reduction among AD patients relative to MCI patients and controls), but not in the fornix or uncinate fasciculus. When the vascular disease summary score was entered as an additional covariate, the findings for both WMH and FA remained unchanged.

DISCUSSION

We showed that increased WMH burden is related to decreased DTI-derived FA, suggesting that both capture aspects of white matter structure. However, the relationship of these white matter measurements to cognition or diagnostic group differed. In general, WMH severity, a marker of small vessel cerebrovascular disease, was more consistently related to cognitive function and AD than FA, a marker of white matter microstructural integrity. Specifically, we found that WMH volume in the frontal lobes was associated with poorer memory and that both frontal and parietal WMH volume is elevated among individuals with AD and at risk for AD (i.e., the MCI group). Global FA, on the other hand, in our sample was not associated with either cognitive functioning or with diagnostic group, although there was a non-significant trend for decreased FA among patients with AD and *post hoc* analyses did reveal statistically reliable diminution of FA among AD patients. Our findings suggest that WMH volume is a more sensitive radiological correlate

Table 3. Standardized beta weights and *p* values (in parentheses) for neuropsychological test performance across diagnostic groups

	CVLT Trials 1–5 Free Recall	CVLT Short Delayed Free Recall	CVLT Long Delayed Free Recall	CVLT Recognition (hits – false positives)	Digit Symbol total correct	Trail Making Test A	Trail Making Test B	Digit Span Forward	Digit Span Backward	Rey Figure Copy	Rey Figure Immediate Recall	Rey Figure Delayed Recall	Verbal Fluency: CFL Total	Categorical Fluency: Animals	Logical Memory Immediate Recall	Logical Memory Delayed Recall	Boston Naming Test
Frontal WMH	–0.324 (0.073)	–0.238 (0.100)	–0.423 (0.020)	–0.512 (0.003)	0.285 (0.168)	0.008 (0.946)	0.117 (0.578)	–0.576 (0.040)	–0.389 (0.212)	–0.110 (0.497)	–0.174 (0.371)	–0.041 (0.838)	0.074 (0.700)	–0.009 (0.960)	0.003 (0.986)	–0.069 (0.649)	–0.039 (0.803)
Temporal WMH	0.137 (0.427)	0.123 (0.455)	0.205 (0.235)	0.840 (0.606)	–0.034 (0.889)	0.601 (<0.001)	–0.174 (0.297)	0.473 (0.150)	0.034 (0.930)	–0.040 (0.498)	0.027 (0.885)	0.015 (0.937)	0.161 (0.385)	0.036 (0.831)	0.392 (0.084)	0.514 (0.019)	0.566 (0.013)
Parietal WMH	–0.069 (0.710)	–0.022 (0.902)	0.036 (0.844)	0.162 (0.356)	–0.092 (0.664)	0.117 (0.320)	0.280 (0.216)	–0.332 (0.241)	–0.136 (0.659)	0.025 (0.881)	–0.002 (0.992)	–0.011 (0.960)	–0.335 (0.097)	0.055 (0.762)	–0.298 (0.176)	–0.324 (0.124)	–0.218 (0.314)
Occipital WMH	0.151 (0.279)	0.212 (0.111)	0.128 (0.355)	0.100 (0.447)	–0.211 (0.232)	–0.270 (0.002)	–0.167 (0.220)	–0.037 (0.874)	0.031 (0.907)	0.082 (0.506)	0.000 (0.999)	0.039 (0.797)	0.061 (0.677)	–0.126 (0.360)	–0.216 (0.161)	–0.281 (0.058)	–0.260 (0.088)
FA summary	–0.031 (0.853)	0.052 (0.747)	0.000 (0.999)	0.022 (0.888)	0.294 (0.237)	–0.048 (0.640)	–0.064 (0.678)	–0.402 (0.223)	–0.253 (0.475)	0.122 (0.405)	–0.011 (0.948)	0.048 (0.787)	–0.048 (0.783)	0.167 (0.317)	0.196 (0.181)	0.160 (0.253)	0.068 (0.638)
Relative brain volume	0.045 (0.699)	–0.033 (0.768)	–0.153 (0.188)	–0.038 (0.726)	–0.115 (0.469)	–0.076 (0.289)	0.053 (0.641)	0.111 (0.599)	0.201 (0.374)	–0.033 (0.744)	–0.037 (0.765)	–0.038 (0.322)	0.047 (0.701)	–0.095 (0.404)	–0.034 (0.763)	–0.483 (0.630)	–0.124 (0.269)
Age	–0.238 (0.088)	–0.378 (0.005)	–0.225 (0.105)	–0.246 (0.063)	–0.292 (0.125)	0.269 (0.002)	0.229 (0.069)	0.189 (0.444)	–0.213 (0.242)	–0.271 (0.027)	–0.125 (0.375)	–0.142 (0.322)	0.008 (0.954)	–0.211 (0.124)	0.020 (0.881)	–0.006 (0.965)	–0.093 (0.476)
Education	0.223 (0.045)	0.109 (0.300)	0.220 (0.047)	0.237 (0.025)	0.465 (0.002)	–0.316 (<0.001)	–0.422 (<0.001)	0.117 (0.333)	0.090 (0.646)	0.417 (<0.001)	0.306 (0.009)	0.287 (0.018)	0.336 (0.005)	0.311 (0.005)	0.396 (<0.001)	0.429 (<0.001)	0.413 (<0.001)

Note. Results are from separate multiple regression analyses run for each of the outcomes (columns). Significant effects are emphasized in bold.

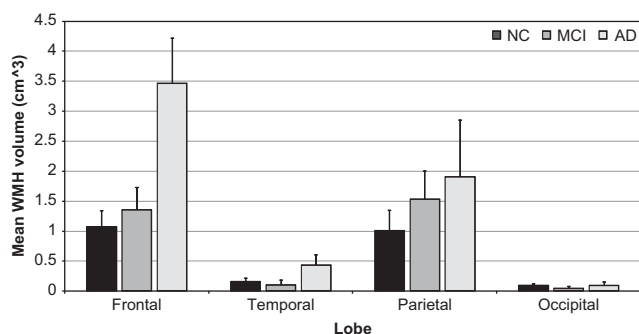


Fig. 4. White matter hyperintensities (WMH) volume differences across diagnostic groups. Error bars are standard errors.

of cognitive functioning among older adults than FA and, particularly when distributed in frontal and parietal lobes, may play a specific role in AD.

Although, to our knowledge, previous studies have not combined macrostructural and microstructural white matter imaging techniques to examine their differential associations with cognition and diagnosis, our finding of a relationship between the two is in line with previous investigations showing an inverse relationship in clinical samples (Engelhardt et al., 2009; Taylor et al., 2001). Despite the shared variance between the two measures, only WMH were related to cognitive function reliably in our study. As FA captures both normal variability in white matter structure as well as disease- or age-related changes (Furutani, Harada, Minato, Morita, & Nishitani, 2005; Grieve et al., 2007; Stricker et al., 2009), the measure may be less sensitive than frank markers of pathology, such as WMH.

It was somewhat surprising that the measures of FA did not emerge as a significant predictor of cognitive function in this study and there are several possibilities for this negative result. First, our interest was in capturing a general measure of white matter integrity. Indeed the derived FA factor accounted for 54.9% in the variance. We expected that these data reduction approach would provide the most reliable general measure of FA that would be related to cognitive function (Penke et al., 2010) but it is possible that subtle regional differences were not captured. Second, our DTI sequences comprised 16 directions, which may have obscured more subtle relationships with cognition. Third, it is possible that among older adults with significant vascular disease histories, measurements of macrostructure that reflect cerebrovascular disease may simply be more relevant to cognitive outcomes than subtle variation in white matter microstructure.

However, we did observe a trend in the data – decreased FA among patients with AD compared to healthy controls – which has been observed in previous studies (Bozzali et al., 2002; Takahashi et al., 2002). Findings have not been entirely consistent, though, particularly with regard to the regional distribution of FA reduction in AD; reduced FA among AD patients has been reported in several regions, including periventricular frontal white matter (Choi, Lim, Monteiro, & Reisberg, 2005), posterior cingulate (Yoshiura et al., 2002),

columns of the fornix (Ringman et al., 2007), thalamus, parietal white matter, posterior limbs of the internal capsule (Rose, Janke, & Chalk, 2008), and genu of the corpus callosum (Salat et al., 2005). Thus, while reduction in FA among patients with AD has been observed, there is a relative paucity of replication regarding specific regions; our findings suggest that when overall white matter microstructural integrity is estimated, there is little evidence of a statistically reliable general reduction among patients with AD.

Our findings are consistent with the increased regional distribution of WMH in frontal and parietal lobes, also found by Yoshita and colleagues (Yoshita et al., 2006) as well as by Leys and colleagues (1991) among patients with AD. These areas are typically associated with memory and are known to be susceptible to AD pathology (Brun & Englund, 1981; Laakso et al., 1995). In the context of AD, WMH may result from perfusion abnormalities, vascular burden, and from vascular deposition of beta amyloid (Brickman et al., 2009), or possibly from Wallerian degeneration to cortical-cortical fiber connections. Frontal and parietal lobes are more vulnerable to perfusion abnormalities (Matsuda, 2001) and vascular deposition of beta amyloid (Esiri & Wilcock, 1986) than the remaining regions of the human brain. This consistent regional distribution of WMH suggests a possible pathological link of AD with vascular disease on a mechanistic level, on the one hand, and/or suggests that a cerebrovascular disease burden in addition to “primary” AD pathology can contribute to the clinical presentation of AD, on the other.

While several studies have reported associations between WMH and cognition (Dufouil, Alperovitch, & Tzourio, 2003; Smith et al., 2011), the specific relationship between WMH and memory performance we observed is not entirely consistent with previous studies. Among neurologically healthy older adults, WMH are typically reported to be related with speeded tasks of executive function (Gunning-Dixon & Raz, 2000). However, there is an emerging literature linking WMH to MCI and AD, which are characterized primarily by an amnesic syndrome (Smith et al., 2011). The current study is consistent with previous reports, which have shown that WMH are not only more common in AD patients, but their appearance is also elevated in people with MCI (Delano-Wood et al., 2009; Luchsinger et al., 2009; Yoshita et al., 2006).

Results from the current study may reflect the unique sample of exclusively African American participants. Increased prevalence and incidence rates of dementia and cognitive dysfunction among older African Americans (Gurland et al., 1999; Perkins & Schisterman, 2006; Tang et al., 2001; Unverzagt et al., 1996) may be due in part to increased cerebrovascular disease among this population (Brickman, Schupf, et al., 2008; Reitz et al., 2009), though previous studies have not found differential brain-behavior relationships across ethnic/racial groups (DeCarli et al., 2008). Future studies should further explicitly examine whether the mediators of cognitive function and diagnostic group vary as a function of ethnic/racial group. Relatively poor specificity of neuropsychological measures used to measure cognitive function and diagnosis patients among

African Americans may be another important source of variance in our study, contributing to both relatively weak associations between the MRI-derived measures of white matter and cognition and to differences between our study and results reported in the extant literature. Mapping the longitudinal course of cognitive change would certainly contribute to a more clear understanding of the link between white matter abnormalities and progressive cognitive change.

There are weaknesses in the current study that are important to highlight. First, the number of statistical comparisons was quite high, increasing the likelihood of Type I statistical error. On the other hand, the number of AD and MCI participants was relatively low, possibly masking group differences due to diminished power and potentially increasing the Type II statistical error rate. Replication of our findings in a separate and larger cohort is clearly warranted. A group of participants did not clearly meet criteria for MCI, AD, or normal cognition and were thus labeled “cognitively impaired not MCI.” It is unclear what the nature of the cognitive impairment is and it is possible they have had cognitive difficulties for most of their adult lives. Again, longitudinal follow-up of participants will be critical to elucidate better whether this subgroup of participants have a neurodegenerative condition. Furthermore, because we were interested in understanding the relationship between imaging markers and cognition or diagnosis and to maintain consistency with the parent study, we did not use the neuroimaging data in the diagnostic formulation of each subject. Future studies may wish to incorporate radiological data (e.g., presence of infarct, regional atrophy) into the diagnostic procedures. Finally, future studies may wish to consider other DTI metrics, which may provide complementary information or may increase sensitivity for detection of relationships between cognition and white matter microstructure.

In summary, we showed that among African American older adults, FA and WMH are associated with each other, but that only WMH were significant predictors of memory and AD diagnosis.

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