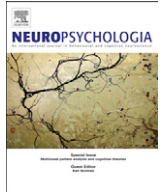


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The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging

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ABSTRACT

Although aging is associated with changes in brain structure and cognition it remains unclear which specific structural changes mediate individual cognitive changes. Several studies have reported that white matter (WM) integrity, as assessed by diffusion tensor imaging (DTI), mediates, in part, age-related differences in processing speed (PS). There is less evidence for WM integrity mediating age-related differences in higher order abilities (e.g., memory and executive functions). In 165 typically aging adults (age range 54–89) we show that WM integrity in select cerebral regions is associated with higher cognitive abilities and accounts variance not accounted for by PS or age. Specifically, voxel-wise analyses using tract-based spatial statistics (TBSS) revealed that WM integrity was associated with reasoning, cognitive flexibility and PS, but not memory or word fluency, after accounting for age and gender. While cerebral fractional anisotropy (FA) was only associated with PS; mean (MD), axial (AD) and radial (RD) diffusivity were associated with reasoning and flexibility. Reasoning was selectively associated with left prefrontal AD, while cognitive flexibility was associated with MD, AD and RD throughout the cerebrum. Average WM metrics within select WM regions of interest accounted for 18% and 29% of the variance in reasoning and flexibility, respectively, similar to the amount of variance accounted for by age. WM metrics mediated ~50% of the age-related variance in reasoning and flexibility and different proportions, 11% for reasoning and 44% for flexibility, of the variance accounted for by PS. In sum, (i) WM integrity is significantly, but variably, related to specific higher cognitive abilities and can account for a similar proportion of variance as age, and (ii) while FA is selectively associated with PS; while MD, AD and RD are associated with reasoning, flexibility and PS. This illustrates both the anatomical and cognitive selectivity of structure-cognition relationships in the aging brain.

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1. Introduction

The neurobiologic underpinnings of age-related cognitive decline remain unclear. Although cerebral atrophy and neuronal death occur in select brain regions during specific diseases (e.g., hippocampal cell loss in Alzheimer's disease), it appears that a majority of non-specific age-related cerebral volume loss is the result of reduced neuronal complexity and loss of connections (Fjell & Walhovd, 2010). Since the coordinated activity of both local and global neural networks relies on cortical-cortical connections, white matter (WM) integrity, i.e., the "intactness" of cortical connections, must be essential for normal cognitive function and loss of WM integrity likely contributes to

age-related cognitive decline (Bartzokis et al., 2004; Deary, Penke, & Johnson, 2010).

Age-related cognitive decline is observed in many domains important in the maintenance of everyday function including memory, executive function and processing speed (PS) (Hedden & Gabrieli, 2004). While reliance of higher order abilities on PS is complex (Park & Reuter-Lorenz, 2009), it has been hypothesized that reductions in PS may account for much of the age-related cognitive change in higher order abilities (Finkel, Reynolds, McArde, Hamagami, & Pedersen, 2009; Salthouse, 1996, 2010). Thus we sought to determine if WM integrity is related to higher order cognitive abilities after accounting for age or PS, and whether WM integrity mediates the associations between higher order cognitive abilities, age and PS.

Both higher order abilities (e.g., executive function and episodic memory) and PS have been variably associated with WM integrity

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(Gold, Powell, Xuan, Jicha, & Smith, 2010; Kennedy & Raz, 2009; O'Sullivan et al., 2001; Turken et al., 2008; Vernooij et al., 2009). However, few studies have tried to determine if reduced WM integrity accounts for the association between higher order abilities and PS. Bucur et al. (2008) reported that WM integrity in prefrontal regions partially mediates the association between PS and episodic memory while Salami, Eriksson, Nilsson, and Nyberg (2011) reported that although WM integrity partially mediates the association between age and PS, it is not strongly related to age-related changes in higher cognitive functions (Bucur et al., 2008; Salami et al., 2011). Thus it remains unclear if WM integrity mediates the association between age-related changes in higher order abilities and declining PS (Madden, Bennett, & Song, 2009a).

Age-related changes in WM integrity (i.e., microstructure) can be assessed with diffusion tensor imaging (DTI). DTI allows for the in situ assessment of WM integrity since water diffuses more freely parallel to myelinated axons (i.e. axial diffusivity (AD)) than perpendicular to them (i.e., radial diffusivity (RD)) (Le Bihan, 2003). Fractional anisotropy (FA) is essentially the ratio of AD to RD while mean diffusivity (MD) is the average diffusion across all directions. Major WM tracts have high FA. Loss of WM integrity is typically defined by reduced FA, perhaps reflecting the loss/degeneration of axons, and increased MD, perhaps reflecting demyelination and loss of parenchymal complexity (Jones, 2008). Aging is associated with decreasing FA and increasing MD throughout much of the cerebral WM (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Burzynska et al., 2010; Damoiseaux et al., 2009; Madden, Bennett et al., 2009; Sullivan & Pfefferbaum, 2003) that is linearly related to average cortical thickness (Kochunov, Glahn, Lancaster et al., 2011). While AD and RD have also been shown to increase with age (Michielse et al., 2010) it is less clear how they are related to cognitive changes during typical aging (Madden et al., 2012). Some evidence points to greater RD changes with aging than AD (Burzynska et al., 2010) while others report equal or greater AD changes (Sala et al., 2010).

Herein we examine where higher order cognitive abilities and PS are associated with WM integrity and whether regional WM integrity mediates the associations between higher order abilities, PS and age. This is important because if changes in WM integrity can explain the association between PS and age-related cognitive decline, it would suggest that WM pathology, and not cell loss, account for cognitive changes during typical aging. To determine where higher order abilities and PS are associated with WM integrity we used tract based spatial statistics (TBSS), a 3D voxel-wise approach that assesses local maximum DTI values (the presumed core of cortical WM tracts (Smith et al., 2006)). We hypothesize that PS will be more strongly and globally related to WM integrity than higher order abilities (Wen et al., 2011) and that executive abilities will be most related to WM integrity in the frontal lobes. In addition, given that flexibility is more associated with PS than other higher order abilities (Schaie, Dutta, & Willis, 1991) we predict that flexibility may be more related to WM integrity than other higher order abilities. To determine if WM integrity can account for the associations between higher order abilities, PS and age, mediation analysis using average regional WM metrics is used. In mediation analysis three conditions must be met (Baron & Kenny, 1986); (i) the cognitive abilities must be correlated with age and PS, (ii) WM integrity must be correlated with age and PS and (iii) WM integrity should account for significant variance in multiple regressions that include the "mediated" variable. This approach has been used in prior studies (Bucur et al., 2008; Madden, Spaniol et al., 2009; Salami et al., 2011) although the mediation effects of WM integrity on age were not explored (Bucur et al., 2008) or only found for PS and not higher order abilities (Madden, Spaniol et al., 2009; Salami et al., 2011). Finally, we hypothesize that WM integrity will account for

unique variance in cognitive abilities beyond that explained by either age or PS.

2. Materials and methods

2.1. Participants

The present study involved 188 subjects who were selected to undergo MRI in 2006–2007 from the Seattle Longitudinal Study (SLS), a cohort-sequential longitudinal study of the relationship between aging, health, cognition and life-style (Schaie, 2005). Imaging data from 165 subjects was used secondary quality control measures (see *Image Analysis* below). SLS members at recruitment represent a stratified-by-age and gender sample from the Group Health Cooperative of Puget Sound, a large HMO in western Washington State. This study has been approved by the University of Washington Medical Center and the Group Health Cooperative of Puget Sound Institutional Review Boards. Participants were selected from the larger group sample ($n=572$) of SLS subjects who had been cognitively assessed in middle age; selection criteria were; (i) had undergone 2 or more cognitive assessments in midlife and/or old age, (ii) participated in the 2005 SLS data collection, and (iii) were willing and capable of undergoing MRI. A vascular risk score (0 to 3) was assigned to each subject based on self-reported diagnoses of hypertension, diabetes or hyperlipidemia (each risk factor being given an equal weight of 1 point). APOE genotyping was performed at Northwest Lipid Research Laboratories (Seattle WA, USA).

2.2. Cognitive assessment

SLS participants were assessed on a broad battery of psychometric abilities in two, 2.5-hour sessions (Schaie, 2005; Schaie, Willis, & Caskie, 2004). Cognitive testing was performed independently of the MRI and occurred on average 24 weeks prior to scanning (s.d. 34 weeks, range 2 years prior to 1.25 years after). The testing-MRI interval was not correlated with age ($r=-0.01$), any DTI metric (all p values > 0.05 , uncorrected for multiple comparisons) or any other demographic factor. However, the testing-MRI interval was correlated with immediate recall (partial correlation $\rho=-0.28$ $p < 0.01$), delayed recall ($\rho=-0.23$ $p < 0.01$), word fluency ($\rho=-0.23$ $p < 0.01$), cognitive flexibility ($\rho=-0.16$ $p < 0.05$) and PS ($\rho=-0.28$ $p < 0.01$) but not reasoning, after accounting for age and gender. This suggests that at any given age at scanning, those taking the test earlier (i.e., prior to the MRI) had slightly better scores than those scanned later (i.e., after the MRI) as expected if scores decline with age.

All subjects were cognitively normal based on neuropsychological assessment and consensus review (MMSE ranged from 24–30 with 2 individuals scoring 24 and one individual scoring 25). Two measures of episodic memory (immediate and delayed recall), word fluency, two measures of executive function (reasoning and cognitive flexibility), and a measure of PS were used in this analysis. All cognitive measures were converted into t-scores using first occasion data from the entire SLS sample for standardization to permit quantitative, longitudinal comparisons across measures with different metrics (Schaie, Willis, & Pennak, 2005).

2.2.1. Episodic memory

Both immediate and delayed recall measures were used (Zelinski, Gilewski, & Schaie, 1993); (Zelinski & Kennison, 2007). For immediate recall, participants studied a 20-word list for 3.5 min followed by 3.5 min of free recall. Delayed recall involved free recall after 1-hour of interim activities (test-retest reliability $r=0.7$) (Zelinski & Lewis, 2003). Words correctly recalled are scored. Immediate and delayed recall are highly correlated ($r=0.92$, $p < 0.001$) and generated qualitatively identical results in all analyses. Combining immediate and delayed recall into a factor score resulted in qualitatively identical results to each individual score, e.g., DTI parameters were not associated with the factor score.

2.2.2. Word fluency

The Primary Mental Abilities (PMA) word fluency test (Thurstone & Thurstone, 1949) requires participants to recall as many words as possible according to a lexical rule in a 5-minute period (e.g., words starting with the letter "S"). In factor analytic work it has been shown to load on verbal memory and ability (Schaie et al., 1991). No factor score for word fluency is available as factor analysis has shown that word fluency is a complex ability with loading on memory, verbal and speed factors (Willis, unpublished results).

2.2.3. Reasoning

The PMA reasoning test (Thurstone & Thurstone, 1949) requires participants to view a series of letters (e.g., abXcdXefXghX...) that are arranged according to one or more rules. Participants are asked to discover the rule(s) and mark the letter that should come next in the series. In the preceding example, normal alphabetical progression is interrupted with an "x" after every second letter and the solution would be the letter "i". Scores represent the number of items (out of 30) that are

answered correctly within a time limit of 6 min. The PMA reasoning test is highly correlated with a reasoning factor score ($r=0.88$) that is composed of PMA reasoning, the ADEPT Letter Series (Blieszner, Willis, & Baltes, 1981) and number and word series measures (Schaie, 2005).

2.2.4. Cognitive flexibility

A factor score was derived from two timed measures in the *Test of Behavioral Rigidity* (Schaie, 2005): (i) the Capitals test (Cap-R score): in which the number of words copied from a paragraph is compared to when subjects copy the same paragraph substituting capitals for lower case letters (and vice versa) and, (ii), the Opposites test (Opp scores): in which subjects respond to three lists of simple words (list 1–3 (L1–3), 40 words/list) by first giving antonyms (L1), then synonyms (L2), and finally antonyms or synonyms depending on whether the stimulus word is printed in upper or lower case letters (L3). The Opp-R1 score represents the ratio of correct to total responses during L3 while, the Opp-R2 score is the ratio of correct responses in L3 compared to the correct responses in L1 and L2. Cognitive flexibility is calculated with the following equation {flexibility= $0.25 \times \text{Cap-R} + 0.35 \times \text{Opp-R1} + 0.40 \times \text{Opp-R2}$ }.

2.2.5. Processing speed (PS)

A factor score was derived from three timed measures (Ekstrom, French, Harman, & Dermam, 1976; Schaie, 2005): (i) identical pictures requires the subject to identify which of five numbered shapes or pictures in a row is identical to the model at the left of the row (number correct out of 50 items in 1.5 min); (ii) Finding A's requires the subject to identify the 5 words in a column of 40 words that contain the letter "a" (number correct out of 50 items in 1.5 min); and (iii) number comparison requires the subject to inspect pairs of multi-digit numbers and indicate whether the numbers in each pair are the same or different (number correct out of 40 items in 1.5 min). PS is calculated by averaging the normalized values for each of the three tests.

2.3. Image acquisition

All scanning was performed on a Philips 3T Achieva scanner. The DTI scan consisted of a single-shot echo-planar sequence with the following parameters: TR/TE/flip angle: 10.5 s/63 ms/90°, a matrix size of 128 × 128, a FoV of 240 × 240 with a 2 mm slice thickness. Diffusion weighting consisted of 32 non-collinear gradient directions, a non-diffusion weighted b_0 map and a b -factor set at 1000 s/mm². Magnetization prepared rapid gradient echo (MPRAGE) imaging was performed using the following parameters; TR/TE/flip = 7 ms/3.2 ms/8°; a matrix size of 240 × 240 and with 160 sagittally collected slices and a slice thickness of 1 mm. FLAIR images were performed with a TR/TE/flip of 11 s/125 ms/90°, respectively; with full coverage of the cerebrum using 0.86 × 0.86 × 3 mm transverse slices.

2.4. Image analysis

DTI: For quality control DTIPrep (Liu et al., 2010) was used to correct for eddy-currents and head motion artifacts and to perform slice-wise intensity related artifact and gradient-wise checking. DTI scalar indices are estimated using the DTIProcess toolkit (www.niral.unc.edu). After this process 33 of the 188 data sets were rejected for having more than 20% bad directions resulting in data analysis being done on a total of 165 subjects. There were no significant differences in age, gender, or measures of health between subjects who were excluded from DTI processing and those included. FMRIB's Diffusion Toolbox (FDT version 2.0) and Tract-Based Spatial Statistics (TBSS) were used to perform voxel-wise analysis of the DTI data (Smith et al., 2006). Preprocessing included the creation of 3D fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps for each subject. For TBSS, each subject's FA map was brought into a common space using FMRIB's nonlinear registration tool (FNIRT), an average FA skeleton was created and thresholded at 0.2 to exclude large inter-subject variability, and each subject's aligned FA data was projected onto this skeleton by searching perpendicular to the skeleton to find local maxima. Rather than using a standardized template, because of the older age of our study population, transformation matrices were calculated for each subject pair (162 × 161 calculations) and the most anatomically representative subject from our dataset was mathematically identified and used as a template. MD, AD and RD values were mapped onto the template by using the projection vectors from each individual's FA-to-skeleton transformation (Smith et al., 2006).

White matter hyperintensities (WMHs): visual ratings of WMHs were performed in FLAIR images by a blinded fashion by a trained clinician (Bruce R. Swamy) using the 10-point Cardiovascular Health Study (CHS) scale (Yue et al., 1997). Bruce R. Swamy was trained by Dr. Dean K. Shibata who has considerable experience using the CHS scale (Fornage, Debette, Bis, Schmidt, & Ikram et al., 2011; Knopman et al., 2011). The CHS scale reflects actual volume of WMH and has good inter-rater reliability (Kapeller et al., 2003). Automated segmentation of WMH was performed with the open-source Fuzzy Lesion Extractor (FLEX, using default parameters) (Gibson, Gao, Black, & Lobaugh, 2010), a semi-supervised method that employs clustering followed by template based spatial analysis. Each step of the FLEX protocol

including skull stripping, WMH assignment and volume calculation was manually reviewed for quality assurance. Each subject's WMH map was transformed into standard space and mapped onto the TBSS skeleton using the same transformation matrices as applied to DTI metrics. This allows us to determine the location of WMH within the skeleton and the proportion of the skeleton and each sub-region that is affected in each individual by WMH.

Cortical thickness: using MPRAGE images, cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are fully described elsewhere (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). After automatic analysis, the gray/white matter surfaces were checked, edited, and reprocessed to ensure that tissue classification was as accurate as possible. For this manuscript, the average cortical thickness was obtained by calculating a weighted average of the 68 parcels defined by the Desikan atlas (Desikan et al., 2006). All processing was performed blinded on de-identified data.

Brain volumes. Using MPRAGE images, brain volumes were calculated using SIENAX which is part of the FSL toolbox (Smith et al., 2002, 2004). Briefly, brain tissue volume, normalized for subject head size, was estimated by extracting brain and skull images. The brain image was then affine-registered to MNI152 space (Jenkinson, Bannister, Brady, & Smith, 2002) in order to obtain the volumetric scaling factor used in head size correction. Next, tissue-type segmentation with partial volume estimation was carried out (Zhang, Brady, & Smith, 2001) in order to calculate the total volume of brain tissue. In a similar fashion, gray and white matter volumes were calculated using FAST which is part of the FSL toolbox (Smith et al., 2004; Zhang et al., 2001).

2.5. Statistical analysis

Descriptive statistics, pairwise and partial correlations and hierarchical analysis were calculated with STATA 10. Average values for each DTI metric were calculated within the TBSS skeleton (99,336 voxels = 99 cm³) or selected regions of interest (ROIs). For ROI analysis, the group average TBSS skeleton was overlaid with tracts from the JHU WM tractography atlas (Mori, Wakana, Van Zijl, 2005) provided in the FSL package; thus the ROIs represent TBSS aligned skeletal regions, not simple untransformed WM regions. These skeletal regions were edited to make them non-overlapping and chosen specifically for their anatomical connectivity (Fig. 1A). ROIs are inclusive regions and do not represent individual WM tracts but rather anatomic WM regions. Given the non-Gaussian distribution of WMH burden in the left anterior thalamic radiation (ATR) across subjects (73% of subjects with no WMH volume, 13% of subjects with < 1% WMH volume, 9% of subjects with < 10%

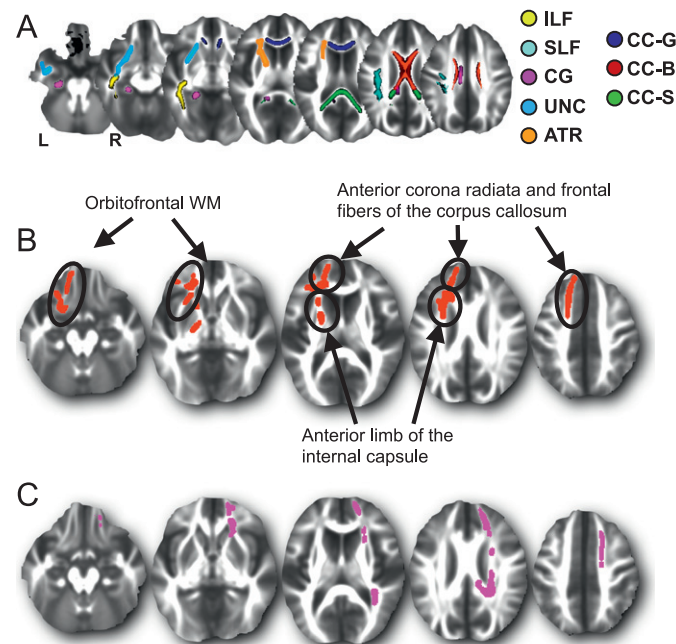


Fig. 1. (A) Skeletal WM regions of interest (ROI). Areas are shown in the left hemisphere only except for regions of the corpus callosum. Inferior and superior longitudinal fasciculi (ILF and SLF), cingulate gyrus (CG), uncinate fasciculus (UNC), anterior thalamic radiation (ATR), corpus callosum genu (CC-G), body (CC-B) and splenium (CC-S). (B) Areas where lower reasoning scores are associated with higher skeletal AD after accounting for the effects of age and gender. (C) Areas where lower flexibility scores are associated with higher skeletal AD after accounting for the effects of PS, age and gender. Depicted slices in (B) and (C) are the same and correspond to MNI z-values of -16 mm, -2 mm, 12 mm, 26 mm and 40 mm.

WMH volume, 2% of subjects with < 20% WMH volume, and a single subject with 38% WMH volume), these values were transformed by taking the square root of the percentage prior to using them as an independent variable. Qualitatively similar results were obtained using non-transformed data.

Hierarchical regressions were performed to determine (i) what proportion of the association between age and each cognitive ability was mediated by WM integrity, (ii) what proportion of the association between PS and each cognitive ability was mediated by WM integrity, and (iii) whether WM integrity continued to be significantly associated with higher order abilities if both age and PS were accounted for Table 5. Two modeling approaches were used. Model 1 (Table 5): in partial correlations accounting for age and gender, each WM metric from the 13 ROIs (thus 13 ROIs \times 4 WM metrics=52 values) was screened for a significant association with cognitive measures. Subsequently, each WM metric identified as significantly correlated was included in the model as a IV regardless of the significance of its β values in the final model. Model 2 (Supplementary Table S3): forward stepwise regressions using cognition as the dependent variable with each of the 52 WM metrics with significant β values ($p < 0.05$) were added stepwise as independent variables after accounting for age and gender. This resulted in a single WM metric associated with reasoning and flexibility.

The proportion of a variable (e.g., age) mediated by another (e.g., a WM metric) was determined by calculating the difference between the β value of the variable alone as a predictor (e.g., β_{age}) versus when the other variable is also in the model (e.g., β_{age_WM}) in the equation (%MED = $(\beta_{age} - \beta_{age_WM}) / \beta_{age} \times 100$). Likewise, the attenuation factor (AF) is determined by calculating variance accounted for when the variable alone is a predictor (e.g., R_{age}^2) versus the amount of additional variance explained by the variable in a hierarchical regression (e.g., $\Delta R_{age_WM}^2$) in the equation (AF = $(R_{age}^2 - \Delta R_{age_WM}^2) / R_{age}^2 \times 100$) (Salthouse, 1993). Mediation analysis requires that all variables are significantly correlated in pair-wise comparisons (Baron & Kenny, 1986). Pairwise correlations for age, PS and higher order abilities were all significant (Table 2). Likewise the pairwise correlations between regional DTI parameters used in our hierarchical regressions and age, PS and the higher order ability were highly significant with uncorrected p -values < 0.005 (not shown).

Voxel-wise analysis was performed using FSL's 'Randomize' method, a permutation-based method developed for applications where the null distribution is unknown (Nichols & Holmes, 2002). For all TBSS, 5000 permutations were performed and only voxels with p values < 0.05 (one-sided tests) fully corrected for multiple comparisons are reported unless noted. 3D maps of the DTI metric were used as the dependent variables. Independent predictor variables included cognitive scores, PS, age and gender. Randomize performs a type 1 partial sum of squares analysis and only reports the orthogonal significance level. Thus significant voxels reported for covariates represent areas where the covariate accounts for significant variance after accounting for all other variables in the model. Significant portions of the WM skeleton were thickened in Fig. 1 for easy visualization.

Multiple comparisons were controlled for using a Benjamini & Hochberg (1995) procedure. In this method, p_i values from a given series of statistical tests are ordered from smallest to largest: $p_1 < p_2 < p_3 < \dots < p_m$ where m is the # of tests. p_i is considered significant if $p_i < (i/m) \times \alpha$, where i is the place of p_i in the ordered list and $\alpha = 0.05$. The largest p value (p_m , i.e., the least significant) is tested first and if this test is significant all other tests with lower p values are considered significant. If p_m is not significant, then p_{m-1} followed by p_{m-2} and continuing with p values of decreasing value (increasing significance) are tested per the prior equation until one is found significant or p_1 is reached.

3. Results

3.1. Study participants and the association between cognition, PS and age

Study participants ($n = 165$, Table 1) represent a well educated, largely Caucasian, typically aging population who had no clinically diagnosed cognitive disorder at the time of imaging (e.g. MCI or dementia). Visual WMH ratings were associated with age (ordered logistic regression, pseudo $R^2 = 0.10$, $F = 52.8$, $p < 0.001$) but were generally low with 80% having CHS ratings of 2 or less on a 10-point scale indicative of mild disease (Yue et al., 1997). 73% had a single or no vascular risk factors (hypertension, diabetes or hyperlipidemia). The frequency of APOE $\epsilon 4$ carriers was 31% (heterozygous or homozygous), similar to that reported for Northern European communities from which many of our participants derive (Saunders et al., 1993).

Typical patterns of age-related cognitive decline were apparent for each measure (recall, word fluency, reasoning and flexibility) and PS (Table 2). Older age was associated with lower cognitive scores

and slower PS (negative r -values) while faster PS was associated with higher cognitive scores (positive r -values). Although significantly correlated, individual higher order cognitive abilities other than immediate and delayed recall ($r = 0.92$) accounted for < 20% of the variance in any other ability (r -values 0.22 to 0.44), leaving a majority of the variability unexplained. Word fluency was less highly correlated with age ($r = -0.15$, $p < 0.05$) than other cognitive measures and PS.

3.2. Voxel-wise associations between WM metrics and cognitive measures after accounting for age or PS

To determine if and where in the brain higher cognitive abilities and PS were associated with WM integrity, 3D voxel-wise analysis was performed on the WM skeleton using DTI metrics (FA, MD, AD and RD) as dependent variables and cognitive abilities and/or PS as predictors, with/without age and gender as covariates of no interest. As expected, older age was associated with lower FA and higher MD in 84% and 95% of the WM skeleton, respectively. Age was not associated with higher FA or lower MD in any region. Within regions of age-related changes in FA and MD,

Table 1
Study participants ($n = 165$).

Age (s.d.)	66.9 (7.8)
(range)	(54–89)
% Female	60%
Years education (s.d.)	16.2 (2.5)
% Caucasian	96%
% APOE $\epsilon 4$ carriers	31%
MMSE (s.d.)	29.2 (1.2)
CHS WMH score ^a	
0–2	80%
> 2	20%
# Vascular risk factors ^b	
0 or 1	73%
2 or more	27%
WMH Burden in cm^3 (s.d.)	3.86 cm^3 (5.04)
(range)	0.03–34.08

Mini Mental Status Exam (MMSE); Apolipoprotein (APOE).

^a Cardiovascular Health Study (CHS) WMH scores can range from 0 to 9 with scores between 0 and 2 considered mild (Yue et al., 1997).

^b Vascular risk factors include hypertension, hyperlipidemia, diabetes and smoking.

Table 2
Pearson's correlations (r) between age, processing speed (PS) and higher order cognitive abilities.

	Age	PS	Immediate recall	Delayed recall	Fluency	Reasoning
PS	–0.36**	–				
Immediate recall	–0.26**	0.51**	–			
Delayed recall	–0.24**	0.47**	0.92**	–		
Word fluency	–0.15*	0.62**	0.38**	0.38**	–	
Reasoning	–0.43**	0.64**	0.33**	0.35**	0.44**	–
Flexibility	–0.40**	0.34**	0.29**	0.22**	0.26**	0.44**

Uncorrected

All p -values significant using a Benjamini and Hochberg (1995) approach to controlling for multiple comparisons ($n = 21$ tests).

* $p < 0.05$.

** $p < 0.005$.

both AD (~95% of the voxels) and RD (~98% of the voxels) were increased, with no areas of decreased AD or RD. Thus older individuals had greater AD and RD values that resulted in lower FA and higher MD throughout a vast majority of the WM skeleton. When uncorrected *t*-scores are mapped, higher MD, AD and RD appear to be more significant (i.e., greater uncorrected *t*-values) in a greater proportion of the WM skeleton than decreasing FA values; specifically in regions of the anterior/superior corona radiata (Supplementary Fig. S1). Likewise, prior to covarying for age and gender, higher cognitive ability scores (except word fluency) and faster PS were associated with higher FA and lower MD, AD and RD in a large proportion of the WM skeleton (data not shown). Given the large proportion of voxels significantly associated with age, higher order cognitive abilities and PS when they were modeled alone, no overt localization (e.g., parietal vs. frontal) could be discerned for any variable and maps of these associations are not presented.

To determined if cognitive abilities and PS continued to be associated DTI metrics after accounting for age, models were tested that included age and gender as covariates (Table 3, single regressions). Faster PS continued to be associated with higher FA, and lower MD, AD and RD in overlapping, diffuse regions of the WM skeleton after accounting for age (Supplementary Fig. S2). Neither immediate or delayed recall, nor word fluency, were associated with skeletal WM integrity after covarying for age and gender. For reasoning, select regions containing ~5% of the voxels remained associated with AD. Areas where reasoning was associated with AD included the left uncinate fasciculus and orbitofrontal areas, and the anterior thalamic radiation and frontal fibers of the corpus callosum (Fig. 1B). Akin to PS, higher flexibility scores were related to lower MD, AD and RD in a large percentage (12–36%) of the WM skeleton after accounting for age and gender (Table 3, single regressions). In contrast to reasoning (Fig. 1B), Supplementary Fig. S2 shows that the association of flexibility with WM metrics is not anatomically restricted to the frontal lobe, but dispersed throughout the entire brain. This demonstrates that reasoning and flexibility account for variance in WM integrity beyond that explained by age.

We next determined if WM metrics remained associated with either reasoning or flexibility after accounting for PS in addition to age and gender. When reasoning and PS were modeled together, reasoning no longer accounted for significant WM variability while PS remained associated with WM integrity throughout the brain

Table 3
Voxel-wise associations between WM integrity, higher cognitive abilities, PS and age.

	Higher FA	Lower MD	Lower AD	Lower RD
<i>SRs with age and gender as CVs</i>				
PS	35	32	14	32
Immediate recall	0	0	0	0
Delayed recall	0	0	0	0
Word fluency	0	0	0	0
Reasoning	0	0	5	0
Flexibility	0	28	36	12
<i>MRs with age and gender as CVs</i>				
Reasoning	0	0	0	0
PS	38	19	0	29
Flexibility	0	0	3	0
PS	30	16	1	21
Reasoning	0	0	0	0
Flexibility	0	0	0	0
PS	37	16	0	29

Summary of voxel-wise TBSS analysis. Values represent the % of voxels within the WM skeleton significantly associated with the cognitive measure (one tailed test $p < 0.05$, fully corrected for multiple comparisons). Single regression (SR), multiple regression (MR), covariates (CVs), processing speed (PS).

(Table 3, multiple regressions). In contrast, when flexibility and PS were modeled together, flexibility remained associated with select regions of AD in the right frontal and parietal lobes including areas of the right uncinate fasciculus, anterior thalamic radiation and anterior corpus radiata (Fig. 1C), while PS remained associated with diffuse regions of FA, MD and RD (data not shown). Thus, for reasoning and flexibility, AD appears more closely associated with the ability than the other WM parameters. When all three cognitive parameters (reasoning, flexibility and PS) are modeled together as independent variables, only PS continues to explain unique variance in FA, MD and RD after controlling for age and gender (Table 3).

3.3. Correlations between regional DTI parameters age, cognitive abilities and PS

Average skeletal WM metrics were associated with PS and flexibility after accounting for age and gender (Supplementary Table S1) directly mirroring our voxel-wise analysis. To determine if regional WM integrity mediated the associations between reasoning, flexibility, age and PS, average WM metrics were extracted from skeletal areas corresponding to the major white matter tracts of the frontal lobes and the corpus callosum. These regions were chosen a priori given the association of the prefrontal cortex with executive function (Salthouse, 2011) and included the (i) cingulum (CG) (ii) the inferior and superior longitudinal fasciculi (ILF and SLF), (iii) the uncinate fasciculus (UNC), (iv) the anterior thalamic radiation (ATR) and (v) the genu, body and splenium of the corpus callosum (CC-G, CC-B and CC-S, see Fig. 1A).

Older age was associated with lower FA and higher MD, AD and RD in every WM ROI (uncorrected *p*-values of Pearson's $r < 0.005$, data not shown). After accounting for age and gender, PS was associated with WM in multiple regions (Supplementary Table S2) with ventral areas (e.g., UNC, ILF, and ATR) appearing to be more highly associated dorsal areas (e.g., SLF and CG). After correcting for multiple comparisons, only WM parameters in the right ILF and left ATR remained significantly associated with PS. Given our findings with voxel-wise TBSS we opted to restrict our analysis with reasoning to ROI AD values since other parameters were not found to be associated with reasoning ($n = 13$ correlations). After accounting for age and gender, reasoning was associated with AD in the left UNC, left ATR and right ILF (Table 4, Regions I). Analogously, we restricted our analysis with flexibility to average MD, AD and RD ($n = 13 \times 3$ correlations). After accounting for age and gender, flexibility was found to be associated with multiple areas of MD, AD and RD in no obvious pattern (Table 4, Regions II). The association between regional AD values and reasoning did not survive correction for multiple comparisons while several regional MD and AD values did remain associated with flexibility using a HB procedure to correct for type 1 error.

3.4. The ability of WM integrity to mediate the effects of PS and age on reasoning and flexibility

To determine if WM parameters identified in our correlation analysis (Section 3.3) could mediate variance in reasoning and flexibility explained by age and PS, we performed a series of hierarchical regressions. The maximum amount of variance in reasoning and flexibility that could be accounted for by WM metrics was determined by using WM integrity values from all the regions identified in the correlational analysis with an uncorrected $p < 0.05$. Thus for reasoning, 3 AD regions (Regions I, Table 4), and for flexibility, 16 WM parameters (Regions II, Table 4) were used in the models. We found that WM regions II accounted for more of the variance in flexibility (29%) than WM regions I did for reasoning (18%, single regressions in Table 5).

Table 4
Partial correlations (ρ) of regional DTI parameters with higher order cognitive abilities.

	Region	Partial correlation	p value
Reasoning (Regions I)	L.ATR AD	-0.20	0.012
	R.ILF AD	-0.19	0.013
	L.UNC AD	-0.18	0.025
Flexibility (Regions II)	L.SLF MD	-0.19	0.013*
	R.CG MD	-0.20	0.013*
	R.ATR MD	-0.19	0.013*
	R.ILF MD	-0.19	0.015*
	L.UNC MD	-0.17	0.026
	L.ILF MD	-0.16	0.044
	R.ILF AD	-0.25	0.001*
	R.ATR AD	-0.21	0.008*
	L.SLF AD	-0.21	0.008*
	L.ILF AD	-0.19	0.014*
	L.UNC AD	-0.19	0.015*
	R.CG AD	-0.17	0.030
	R.CG RD	-0.20	0.011
	R.ATR RD	-0.18	0.020
	L.SLF RD	-0.18	0.024
L.UNC RD	-0.16	0.044	

Partial correlations of reasoning and flexibility with regional MD, AD and RD after controlling for the effects of age and gender. Only regions with $p < 0.05$, uncorrected for multiple comparisons, are listed. See Fig. 1 for anatomical abbreviations.

* Significant after BH procedure for controlling for multiple comparisons.

However, for both abilities, WM regions mediated ~50% of the variance attributed to age but a different proportion of the variance attributed to PS, 11% for reasoning and 44% for flexibility (hierarchical regressions in Table 5). Finally, when WM regions, PS, age and gender are all included in the model, 44% of the variance in reasoning and 34% of the variance in flexibility can be explained (multiple regression in Table 5). For WM metrics included in regions II, we explored if regional MD ($n=6$), AD ($n=6$) and RD ($n=4$) explained differing amounts of variance in flexibility. No dramatic differences were found; with $R^2=0.225$ $F=6.5$ for MD values; $R^2=0.249$ $F=7.4$ for AD values; and $R^2=0.211$ and $F=8.5$ for RD values.

Similar results were found using forward stepwise regressions to identify WM regions accounting for significant variance in reasoning and flexibility. Herein, reasoning or flexibility was used as the dependent variable and all 52 DTI parameters were screened as possible predictors in a stepwise fashion (4 DTI metrics \times 13 regions) after inclusion of age and gender as covariates. We found that AD in single ROIs, the left ATR for reasoning and the R. ILF for flexibility could account for 14% and 21% of the variance in reasoning and flexibility, respectively (SRs in Supplementary Table S3). Similar to our results using multiple regions above, AD accounted for a similar amount of variance in reasoning (30%) and flexibility (38%) attributed to age, but less of the variance in reasoning (7%) than flexibility (40%) attributed to PS. Importantly, and in contrast to prior reports (Salami et al., 2011), the β values for these individual DTI parameters remained significant in the models after including PS. When individual WM metrics, PS, age and gender were all included as predictors, the WM metric continued to account for significant variance in flexibility but not reasoning as illustrated by their significant β values in the final multiple regression (MRs in Supplementary Table S3).

3.5. White matter hyperintensities and cognition

As discussed, our typically aging sample is relatively healthy with a low incidence of cardiovascular risk factors and few WMH (Table 1). To assess the role of WMH in cognition, WMH were

Table 5
Hierarchical regressions evaluating the mediation effects of DTI metrics on the association between PS and cognitive measures.

DV	IVs	β	R^2	F -value	ΔR^2	%MED	AF	
Reasoning	SR	Regions I	n.a.	0.183	9.0			
		Age	-0.398**	0.160	15.4			
		PS	0.620**	0.389	64.1			
	HR	Regions I	n.a.					
		Age	-0.210*	0.210	8.4	0.027	47%	83%
		Regions I	n.a.					
		PS	0.553**	0.435	24.2	0.252	11%	35%
		MR	Regions I	n.a.				
			PS	0.539**				
	Flexibility	SR	Regions II	n.a.	0.294	4.8		
Age			-0.416**	0.205	20.9			
PS			0.318**	0.133	12.3			
HR		Regions II	n.a.					
		Age	-0.210*	0.321	5.1	0.027	50%	87%
		Regions II	n.a.					
		PS	0.178*	0.310	5.0	0.016	44%	88%
		MR	Regions II	n.a.				
			PS	0.153*				
		Age	-0.200*	0.340	5.1			

ΔR^2 represents the change in R^2 when age (or PS) is added to the model after the WM metric. %MED is the % of the age (or PS) effect mediated by the WM metric. The attenuation factor (AF) represents the % reduction in the amount of variance explained by age (or PS) when WM metrics are added to the model first. Single regression (SR); hierarchical regression (HR); multiple regression (MR); processing speed (PS). See Table 4 for anatomical abbreviations. All F -values have $p < 0.01$. All models include gender as a CV of no interest

* $p < 0.05$.
** $p < 0.005$.

mapped in each individual using automated segmentation (Gibson et al., 2010). WMH burden (i.e., volume) was significantly associated with age ($F_{1,185}=39.2$, $p < 0.001$, $\text{adj}R^2=0.17$) with ventricular end-capping found in ~15% of subjects and periventricular hyperintensities in ~10% (Supplementary Fig. S3). Total WMH burden was not significantly associated with any cognitive variable after accounting for age and gender ($F_{3,161}$ and β values for the WMH term were never significant with $p > 0.1$). However, multiple regressions revealed that greater WMH burden was associated with lower skeletal FA and greater skeletal MD, AD and RD after accounting for age and gender (Supplementary Table S4). Individual subject's WMH maps were then transformed onto the standard space WM skeleton (see methods). In voxel-wise analysis, age was associated with WMH throughout the WM skeleton (data not shown) while none of our higher cognitive abilities or PS was significantly associated with WMH after accounting for age.

To control for WMH burden in the mediation analysis, we calculated the percent of each ROI affected by WMHs. Only the bilateral ATRs, which lie anterior-lateral to the frontal horns of the lateral ventricles, i.e., the regions were periventricular end capping occurs, had $> 1\%$ WMH in more than 10 subjects. Given this, regional WMH burden could not be accurately modeled in our regressions since most subjects had a trivial burden. Excluding subjects with $> 1\%$ WMH burden in any individual ROI in the reasoning and flexibility regressions reported in Table 5 and Supplementary Table S3 had no meaningful impact on the significance or interpretation of the models (data not shown). In the left ATR WMH burden ranged from 0 to 37% with 119 subjects having no WMHs and the average burden within 44 subjects with WMH being ~4% (s.d. 6%) of the ROI. Including left ATR WMH burden in regressions with reasoning as the dependent variable as done in Supplementary Table S3 increased the significance of left ATR AD in predicting reasoning. In MRs with reasoning as dependent variable, $\beta_{L.ATR AD} = -0.074$, $p = 0.32$ (see Table 5); while

after inclusion of WMH burden as a covariate, $\beta_{\text{L}^{\text{ATR}}_{\text{AD}}} = -0.217$, $p < 0.05$ ($F_{\text{model}} = 25.8$, $R^2 = 0.45$).

3.5.1. Gray matter volume, cortical thickness and cognitive abilities

The relationship between brain volumetric measures, cognition and DTI metrics was explored. Flexibility was the only cognitive variable significantly correlated with either raw or intracranial volume (ICV) corrected cerebral volumes (Supplementary Table S5). The partial correlation of flexibility, after accounting for age and gender, with ICV adjusted GM volume was $\rho = 0.16$ ($p < 0.05$) and given that 36 correlations were performed we believe this may reflect type I error. In contrast, GM thickness, volume and brain volume, but not WM volume (excluding FA), were all highly associated with DTI metrics. After controlling for age and gender, greater brain or GM volume is associated with higher FA and lower MD, AD and RD (Supplementary Table S5). Thus larger brain and GM volumes are not directly related to higher cognitive abilities but are related to DTI metrics, suggesting that DTI metrics are more tightly linked to cognitive abilities.

4. Discussion

Cognitive decline during typical aging is highly variable with substantial inter-individual differences. Herein, we examined where WM integrity is related to higher order cognitive abilities and whether it mediates the associations between higher order abilities, age and PS. Overall, we found that after accounting for the effects of age and gender, WM integrity is associated with reasoning, flexibility, and PS but not memory or word fluency. This suggests that WM integrity is important for coordinating function of distant cortical regions during higher cognitive processing. Voxel-wise analysis revealed that the spatial localization of the associations between WM integrity and cognition is variable. Some abilities (e.g., immediate and delayed recall, word fluency) have no significant association with WM integrity, others (e.g., reasoning) are selectively associated with individual DTI metrics in specific regions, while others (e.g. cognitive flexibility and PS) are related to WM integrity throughout the cerebrum. Finally, WM metrics mediated a significant proportion of age-associated variance in reasoning and flexibility but less of the variance associated with PS. In addition to these major findings, several other results are of interest. First, wide spread age-related reductions in FA and increases in MD are both associated with increases in AD and RD. Second, FA was more associated with PS than other cognitive measures. Third, and in agreement with prior reports (Salami et al., 2011), PS appears to be more tightly associated with WM integrity than other cognitive measures, but the exact relationship differs for each cognitive domain. Finally, whole brain volumetric measures and WMHs were related to DTI metrics but not cognition illustrating the centrality of WM integrity in higher cortical function.

4.1. Localization of WM integrity related to higher order cognitive abilities and PS

Voxel-wise analysis revealed that frontal WM integrity was associated with reasoning and flexibility after accounting for age and/or PS. As anticipated by prior work (reviewed in Gunning-Dixon, Brickman, Cheng, and Alexopoulos (2009), Madden et al. (2012), Sullivan and Pfefferbaum (2006)) age is a strong predictor of WM integrity and we found that a majority of the WM skeleton demonstrated lower FA and higher MD, AD and RD in older individuals. After accounting for age, select regions of left frontal AD were associated with reasoning while AD, RD and MD throughout the cerebrum were associated with flexibility. Areas

of AD associated with reasoning included regions of commissural fibers (forceps minor), projection fibers (corona radiata), thalamico-cortical fibers (anterior thalamic radiations) and fibers connecting the left ventral prefrontal regions to medial temporal regions (uncinate fasciculus) and thus could underlie many aspects of executive function (see Schmahmann and Pandya (2009)). This is consistent with substantial literature localizing executive function to the prefrontal lobes (Stuss & Knight, 2002) and reports relating prefrontal WM integrity to executive function (Davis et al., 2009; Kennedy & Raz, 2009). The global association of WM integrity with flexibility may reflect the close association of flexibility with PS (Schaie et al., 1991).

After accounting for age, PS remained associated with WM integrity throughout the cerebrum. This is consistent with prior reports demonstrating the strong associations between PS and WM integrity (Kennedy & Raz, 2009; Madden, Spaniol et al., 2009). Furthermore, when age and individual higher order abilities were included as predictors, PS remained variably, but more robustly, associated with DTI metrics than cognitive abilities did (again, with the exception of AD and flexibility). Thus, while accounting for PS and age reduced or entirely accounted for the associations between DTI metrics and higher cognitive abilities, PS continued to variably predict DTI metrics, demonstrating that PS is more tightly linked to WM structure than most other abilities.

Finally, immediate and delayed recall and word fluency were not found to be associated with WM integrity which is consistent with some (Salami et al., 2011; Vernooij et al., 2009), but not other reports (Deary et al., 2006; O'Sullivan et al., 2001). In our sample word fluency was assessed by the number of "S" words generated in 5 min and it was only weakly associated with age, although it was highly associated with PS (Deary et al., 2006; O'Sullivan et al., 2001). In contrast both immediate and delayed recall were moderately correlated with age ($r = 0.24$ and 0.26 , respectively) showing that the lack of association with DTI metrics cannot be solely accounted for by differing age-related changes.

4.2. Regional WM integrity partially mediates the association between age and higher order abilities

Regional WM integrity (i.e., average DTI metrics from within ROIs) accounted for a small proportion of variance in reasoning and flexibility and could mediate ~50% of the variance attributed to age. WM metrics appear to mediate a greater proportion of variance in flexibility than reasoning ($R^2 = 0.29$ and 0.20 , respectively). Areas of AD found to be associated with reasoning include, amongst others, fibers of frontal-striatal circuits of the dorsolateral prefrontal cortex and are likely central to executive function (Saint-Cyr, 2003). That WM metrics in the ILF (both sides) were associated with reasoning and/or flexibility may be due to the centrality of visual processing (e.g., occipitotemporal connections) on our cognitive paradigm.

Of note, after performing voxel-wise analysis with TBSS we did not extract average DTI metrics from the significant regions to perform mediation or other statistical tests, given the multitude of problems interpreting post-hoc statistics from statistically defined regions, especially given the non-independence of our covariates (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009; Vul, Harris, Winkielman, & Pashler, 2009). Thus, our ROIs of the aforementioned areas were drawn from a priori from an anatomical atlas.

4.3. Regional WM integrity partially mediates the association between PS and higher order abilities.

Regional WM integrity mediated a variable proportion of the association between PS, reasoning and flexibility. Declining PS has been proposed to account for a significant proportion of cognitive

decline during typical aging (Finkel, Reynolds, McArdle, & Pedersen, 2007; Salthouse, 1996). Mechanisms underlying this are unknown but have been hypothesized to involve changes in the “scaffolding” or the coordination of large neural systems secondary to multiple insults associated with aging and disease (Park & Reuter-Lorenz, 2009). As expected, PS can account for 62% or 32% of the association between age and reasoning or flexibility, respectively (statistics not shown). Thus WM integrity was unable to explain most of the association between PS and higher order abilities, and accounting for PS did not fully explain the association between reasoning, flexibility and WM integrity.

4.4. Relationship of WM metrics to cerebral volumes and WMH burden

The primary aim of this paper was to explore the relationship of WM metrics with cognition. In the process brain volumes and WMH burden was assessed and we found that neither cerebral volumetric parameters (GM volume, WM volume, and GM thickness) nor total or regional WMH burden was associated with cognitive measures while most of these parameters were associated with WM integrity. There are few reports that examine the relationship of WM integrity, WMH burden and cognition during aging. While cortical thickness and WM integrity is highly correlated across the lifespan (Kochunov, Glahn, Lancaster et al., 2011) and share genetic underpinnings (Kochunov, Glahn, Nichols et al., 2011) there are mixed reports of how these parameters are related to cognition. In a mixed sample of healthy controls and individuals with cognitive impairment, WMH burden was related to cognition while FA summary scores were not (Meier et al., 2012) while GM and WMH volume were related to regional FA (and cognitive status) to a greater extent than FA was related to cognitive status (Lee et al., 2010). In non-demented samples WM metrics appear more strongly associated with cognition than WMH burden (Schivavone, Charlton, Barrick, Morris, & Markus, 2009). Our findings suggest that while volumetric measures and WMH burden are highly related to WM integrity, WM integrity may actually be more proximal to cognitive function.

4.5. Interpreting WM metrics

In voxel-wise analysis, we found that after accounting for age and gender, FA was less associated with higher order abilities than PS, and in contrast with Davis et al. (2009), we found MD, AD and RD to be variably associated with other cognitive abilities and PS. Finally, right cerebral AD was selectively associated with cognitive flexibility after accounting for PS, age and gender. Although anisotropy of water diffusion is known to reflect WM microstructure, with AD more related to axonal properties and RD more related to myelination (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010), the exact histological correlates of FA, MD, AD and RD remain obscure. Axonal loss in SOD1 mice is associated with reduced AD and FA (Underwood, Kurniawan, Butler, Cowin, & Wallace, 2011) and in Wallerian degeneration reductions in AD coincide with axonal injury and increasing RD with demyelination (Sun, Liang, Cross, & Song, 2008). However, in other disease models results are less definitive. For instance, after trauma AD accurately reflected axonal damage but RD was not associated with demyelination (Budde et al., 2007) and in hypoxia AD reflected axonal damage whereas MD was not associated with axonal pathology (Holland et al., 2010). Likewise, in one of the few studies of fresh tissue in humans (Concha et al., 2010), FA accurately reflected density of axonal membranes whereas MD, AD and RD were not clearly associated with any specific histologic measure of WM structure, although there was a trend for RD to be associated with

myelination and intra vs. extra-axonal space. Beyond this, the interpretation AD and RD is further complicated by the density of crossing fibers, WM pathology and partial voluming, all which may impact the biophysical interpretation of the eigen-vectors (Wheeler-Kingshott & Cercignani, 2009).

With this in mind, it is unclear why select regions of AD are more associated with flexibility than PS, whereas diffuse regions of FA and RD are more associated with PS than flexibility. Expansion of the extracellular matrix or loss of WM complexity (Norris, 2001), via reduction of axon collaterals or crossing fibers (Counsell et al., 2006) could lead to higher AD, and this process could be more fundamental for flexibility than PS. Using a similar approach with MD as a dependent variable, Kantarci et al. (2011) have shown that regional cortical MD values are selectively associated with various cognitive domains. In contrast to our results, they report that memory and language are associated with temporal lobe cortical MD whereas no specific cortical associations could be found for executive function or visual-spatial PS.

Declining FA during aging has been largely attributed to increases in RD, more so than decreases in AD (Bhagat & Beaulieu, 2004; Sullivan & Pfefferbaum, 2006) although prior reports using age stratified samples revealed increases in both AD and RD during aging (Bennett et al., 2010; Burzynska et al., 2010). These WM changes are suggested to reflect changes in myelination rather than loss of axons (Madden, Spaniol et al., 2009). In our sample, aging was accompanied by higher, not lower, AD values although proportionally greater increases in RD resulted in the well established decline in FA throughout the cerebral white matter. This pattern of changes may reflect axonal loss, myelin degradation and expansion of the extracellular component (Sen & Basser, 2005). Regions of declining AD in the anterior/superior corona radiata and paricallosal regions of the frontal cortex have also been reported in aging (Bennett et al., 2010). Although we did not find any regions of decreasing AD it is of interest that AD in the anterior/superior corona radiata and pericallosal fibers was specifically associated with reasoning and flexibility. This suggests that while increasing AD in individuals > 65 may be associated with aging and loss of executive function, across the lifespan, when executive functions are maturing (i.e., between age 20 and 65, (Schaie, 2005)) AD is actually diminishing in these same areas. One interpretation of these findings is that reductions in AD prior age 65 may reflect functionally beneficial changes while increases in AD after age 65 reflects degeneration. However, as we have noted, the interpretation of DTI WM integrity parameters is tenuous at this time.

4.6. Study limitations

Limitations to this study are its cross-sectional design, reliance on a single technique (TBSS) to evaluate DTI metrics and the use of valid but atypical measures of cognitive abilities. Cross sectional studies are confounded by cohort effects and thus we cannot unambiguously conclude that the age/cognition associations we have observed truly represent age-related changes. Longitudinal imaging is underway to evaluate this more completely and determine the rate at which FA/MD declines during aging. Our cognitive testing-MRI interval was variable, occurring on average 24 weeks prior to scanning. As would be predicted, at any given MRI age, those tested earlier (who would be younger at testing), scored better than those tested later. However, the testing-MRI interval was not associated with any DTI or volumetric parameter and thus does not change the interpretation of our results. The testing-MRI interval was variable secondary to the complexities of the longitudinal design and MRI scheduling.

We chose to use TBSS for our analysis given the difficulties of appropriately aligning WM structures necessary for group level

voxel-wise analysis. Careful visual inspection of the alignment steps confirmed that it was not possible to “warp” a group level region of interest into subject specific space whereas the TBSS skeleton appeared to accurately reflect individual subjects WM structure in all cases. The Seattle Longitudinal Study has been ongoing since 1956 necessitating the consistency of cognitive metrics employed over the decades and the sample is largely comprised of middle-class Caucasian subjects (Schaie, 2005). In addition, we chose to use average GM and WM volumes rather than regional volumetric parameters because simultaneous analysis of DTI metrics with GM (or WM) variations was felt to be beyond the scope of this paper. Furthermore, although anatomically meaningful, TBSS does not provide connectivity information and thus WM integrity changes found within a region cannot be attributed to specific regions of the cortex. Future work will undoubtedly untangle these complicated regional volumetric-DTI relationships.

Accounting for genetic, demographic and biological factors in this study is difficult. For voxel-wise analysis, gender was included as a covariate of no interest to ensure that reported associations did not reflect gender effects. We did not include gender in our mediation analyses given that it would change reported R^2 and F values, and thus the calculated mediation effects. Controlling for either cortical atrophy or the extent of WMH raises other issues. Both factors are associated with aging and WM metrics. Given this, and similar to other authors (Bucur et al., 2008; Salami et al., 2011), we did not feel it was appropriate to control for either factor in mediation or voxel-wise analysis. Although > 50% of the general population has a least one WMH at age 50 (Wen, Sachdev, Li, Chen, & Anstey, 2009) how they are associated with cognitive decline during typical aging remains unclear (DeBette & Markus, 2010). Fortunately, 80% of our subjects have CHS WMH rating of 2 or less, reflecting rather minimal white matter disease (Yue et al., 1997).

4.7. Summary

These data show that WM integrity is variably associated with higher order cognitive abilities above and beyond that explained by age or PS. Episodic memory, reasoning and flexibility were all significantly related to WM integrity after accounting for age or PS. Voxel-wise analysis confirmed that the associations between reasoning and WM integrity are the strongest in the frontal lobe, whereas flexibility was associated with WM integrity throughout the cerebrum. Moreover, AD appeared more strongly related to higher order abilities than FA or RD and regional AD values could mediate a significant proportion of variance attributed to age or PS. These data demonstrate that loss of WM integrity contributes to cognitive change during typical aging in ways other than its effects on PS and suggests that coordination of distant brain regions via axonal connections is essential for higher order cognitive abilities.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2013.03.005>.

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