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Microstructural white matter changes mediate age-related cognitive decline on the Montreal Cognitive Assessment (MoCA)

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Abstract

Although the relationship between aging and cognitive decline is well established, there is substantial individual variability in the degree of cognitive decline in older adults. The present study investigates whether variability in cognitive performance in community-dwelling older adults is related to the presence of whole brain or tract-specific changes in white matter microstructure. Specifically, we examine whether age-related decline in performance on the Montreal Cognitive Assessment (MoCA), a cognitive screening tool, is mediated by the white matter microstructural decline. We also examine if this relationship is driven by the presence of cardiovascular risk factors or variability in cerebral arterial pulsatility, an index of cardiovascular risk. Sixty-nine participants (aged 43–87) completed behavioral and MRI testing including T1 structural, T2-weighted FLAIR, and diffusion-weighted imaging (DWI) sequences. Measures of white matter microstructure were calculated using diffusion tensor imaging analyses on the DWI sequence. Multiple linear regression revealed that MoCA scores were predicted by radial diffusivity (RaD) of white matter beyond age or other cerebral measures. While increasing age and arterial pulsatility were associated with increasing RaD, these factors did not mediate the relationship between total white matter RaD and MoCA. Further, the relationship between MoCA and RaD was specific to participants who reported at least one cardiovascular risk factor. These findings highlight the importance of cardiovascular risk factors in the presentation of cognitive decline in old age. Further work is needed to establish whether medical or lifestyle management of these risk factors can prevent or reverse cognitive decline in old age.

Descriptors: Aging, Executive function, Older adults, Anatomical (e.g, sMRI, DTI)

White matter disease or leukoaraiosis is believed to result from hardening and restriction of the small arteries that supply deep cerebral white matter and to produce reduced efficiency of neural communication (e.g., Pantoni & Garcia, 1997). These changes in cerebral tissue appear as white matter hyperintensities (WMH) on T2-weighted MRIs. WMH are typically detected as an incidental finding during clinical investigations for transient ischemic attack, stroke, or dementia and are associated with increased risk of stroke and dementia (e.g., Gerdes et al., 2006; Imaizumi, Inamura, & Nomura, 2014; Young, Halliday, & Krill, 2008). However, cerebral white matter changes are also common in healthy older adults who show no clinical signs of dementia (e.g., Madden, Spaniol et al, 2009; Salat, 2011; Sullivan & Pfefferbaum, 2006), especially in the presence of cardiovascular risk factors, such as hypertension and high blood cholesterol (e.g., Liao et al. 1996; Yamauchi, Fukuda, & Oyanagi, 2002; Wong et al., 2002). Despite differences in the methods used to quantify white matter changes and to assess cognitive functioning (Frisoni, Galluzzi, Pantoni, & Filippi, 2007), early studies using volumetric measures or visual ratings of WMH mostly concur that increasing severity of WMH is associated with cognitive decline in otherwise healthy older adults (e.g., De Groot et al., 2000; Gunning-Dixon & Raz, 2003; Prins et al., 2005; Söderlund et al., 2006).

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PSYCHOPHYSIOLOGY

Diffusion tensor imaging (DTI) is an advanced MRI technique that quantifies changes in cerebral white matter that appears normal in conventional T2-weighted MR images, thereby providing a sensitive measure of white matter in neurologically and cognitively healthy older adults. DTI uses the directional dependence of the movement of water molecules to make inferences about the microstructural integrity of white matter (Le Bihan et al., 2001; Mori, 2007). Water molecules within (and outside of) the tissue encounter barriers imposed by cellular structure, and thus diffusion of water molecules will take restricted pathways over time. Since white matter is highly organized into tracts, diffusion is obstructed across tracts resulting in anisotropic diffusion predominantly along the orientation of fiber tracts. Fractional anisotropy (FA) is the most widely cited measure of white matter microstructure. High FA values indicate that diffusion is restricted and more directionally dependent, which is interpreted as indicating a higher level of microstructural integrity of white matter (Basser & Jones, 2002). Studies comparing WMH and DTI measures to quantify white matter structure highlight the greater sensitivity of DTI measures to individual differences in cognitive functioning, and especially processing speed and executive functioning (e.g., Kerchner et al., 2012; Nitkunan, Barrick, Charlton, Clark, & Markus, 2008; O'Sullivan et al., 2004; Salami, Eriksson, Nilsson, & Nyberg, 2012; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012; Shenkin et al., 2005). Indeed, recent studies suggest that changes in white matter microstructure may underlie age-related decline in cognitive function on a range of neuropsychological tasks (e.g., Bendlin et al., 2010; Lopez-Oloriz et al., 2014; Sullivan, Rohlfing, & Pfefferbaum, 2010; Vernooij et al., 2009; Zhuang et al., 2010) and experimental measures that target executive functioning (e.g., Madden, Spaniol et al., 2009; see Bennett & Madden, 2014, for review). Moreover, white matter microstructural changes may explain the greater age-related cognitive decline in the presence of cardiovascular risk factors (Kennedy & Raz, 2009; Maillard et al., 2012). However, it remains to be determined whether the relationship between white matter structure and cognitive decline can be attributed to typical processes that occur with increasing age or represent the emergence of subclinical pathological processes that result from modifiable cardiovascular risk factors. Differentiating between these alternatives is important as it can inform medical or lifestyle approaches to reduce the proliferation of white matter damage and reverse, limit, or delay the onset of cognitive impairment in older adults (Alagiakrishnan, McCracken, & Feldman, 2006; Larson et al., 2006; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001).

In addition to FA, DTI provides measures of both the magnitude (i.e., mean diffusivity, MD) and the direction of diffusivity. Axial diffusivity (AxD) measures principal diffusivity along the main white matter axonal orientation. Radial diffusivity (RaD) measures mean cross-sectional diffusivity across the main white matter axonal orientation. The cellular properties of the neural tissue can differentially alter directional diffusion properties. For instance, axonal damage can increase diffusivity along the principal orientation (i.e., increased AxD; Sun et al., 2006) whereas myelination restricts diffusion across the main orientation (i.e., reduced RaD; Song et al., 2003). Demyelination arising as a consequence of pathology (e.g., in multiple sclerosis, Klawiter et al., 2011; or in shiverer mice, Song et al., 2003) has been associated with increased RaD, presumably reflecting a DTI index of myelination changes. As changes in overall FA can arise from combinations of axonal and myelination changes, measures of diffusion directionality can provide greater insight into white matter changes associated with age and pathology (Alexander, Lee, Lazar, & Field, 2007). Moreover, radial diffusivity at higher diffusion gradients (i.e., $b > 2{,}880$ vs. $b < 1{,}280$, Wu et al., 2011) is the most sensitive DTI measure of changes in myelin content, which is an important factor in the aging process. In fact, aging studies that have used RaD have shown that it is more sensitive than FA and MD to age-related white matter changes (Bennett, Madden, Vaidya, Howard, & Howard., 2010; Davis et al., 2009; Madden, Bennett, & Song, 2009).

In this study, we examine whether performance on a global cognitive screening tool is associated with changes in white matter macrostructure (e.g., WMH) and microstructure (e.g., DTI) in a sample of healthy community-dwelling older adults, when controlling for the effects of age. Previous studies have shown that scores on the MMSE (Folstein, Folstein, & McHugh, 1975) are associated with degree of white matter disruption in both Alzheimer's and small vessel disease patients (Baxter et al., 2006; Bozzali et al., 2002; De Groot et al., 2002; van der Flier et al., 2005). However, the MMSE is not sensitive to early cognitive decline in healthy older adults (Markwick, Zamboni, & de Jager, 2012; Nasreddine et al., 2005). In this study, we use the Montreal Cognitive Assessment (MoCA), which is more sensitive than the MMSE to mild cognitive decline in clinical groups and healthy older people (Aggarwal & Kean, 2010; Markwick et al., 2012; Nasreddine et al., 2005; Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012). We compare different DTI measures to examine whether RaD, a measure affected by demyelination, is a more sensitive predictor of early cognitive decline than other measures of diffusivity. We also compare DTI measures of global and regional (tract-specific) white matter microstructure to determine whether MoCA scores are more sensitive to disruption of total brain microstructure or disruption in specific white matter tracts.

Age-related cognitive and brain changes are more prominent in the presence of cardiovascular risk factors, such as hypertension and high blood cholesterol (Kennedy & Raz, 2009; Maillard et al., 2012; Williams et al., 2013). These risk factors are associated with changes in cerebral vasculature and concomitant changes in cerebral blood flow and pulsatility (Boreham et al., 2004; Jennings et al., 2013; Jolly et al., 2013). For instance, Zimmerman et al. (2014) showed that, in an older adult sample, increasing age was associated with a significant decline in cerebral blood flow in global and parietal gray matter, as well as parietal white matter. Moreover, cardiovascular fitness was strongly associated with both gray and white matter blood flow, even when correcting for age, and mediated the effects of age on cerebral blood flow (Zimmerman et al., 2014; see Bherer, Erikson, & Liu-Ambrose, 2013, for review). Measures of intracranial and intracerebral blood flow pulsatility have also been associated with white matter changes. Lopez-Oloriz et al. (2014) measured middle cerebral artery (MCA) pulsatility index using transcranial ultrasound. MCA pulsatility was weakly associated with FA in clusters in the fornix, thalamic radiation, and corticospinal tract (i.e., did not survive familywise error rate correction). Both MCA pulsatility and mean FA in these clusters were weakly to moderately correlated with cognitive performance in a number of cognitive domains, when controlling for demographic (age, gender, education) and cardiovascular risk factors (diabetes, hypertension). High cerebral blood flow pulsatility measured with MRI has been shown to be associated with macrostructural changes (i.e., white matter hyperintensities) in transient ischemic attack (Webb et al., 2012) as well as patients with idiopathic (Bateman, 2002) or vascular dementia (Bateman, Levi, Schofield, Wang, & Lovett, 2008). In healthy community-dwelling

older adults, Jolly et al. (2013) showed that cerebral arterial pulsatility, but not arterial inflow or any venous measure, was associated with lower FA and higher RaD in white matter, even when correcting for age.[1] That is, the pulsatile quality of arterial blood flow, rather than the volume of this flow, was linked with white matter integrity (Jolly et al., 2013; see Henry-Feugeas & Koskas, 2012). In this study, we examine whether cerebral arterial pulsatility mediates the relationship between white matter microstructure and MoCA scores. Finally, given that the relationship between arterial pulsatility and white matter microstructure has been shown in our current sample to be much stronger in participants with cardiovascular risk factors (Jolly et al., 2013), we examine whether the presence of cardiovascular risk factors moderates the effect of white matter changes on cognitive performance.

Method

Participants

Seventy (35 male) individuals aged 43–87 years were recruited between January 2011 and August 2012. Thirty-five participants were recruited from the Hunter Medical Research Institute volunteer register. The remaining participants were recruited among people who had attended a general neurology clinic for investigation of a possible mild stroke or transient ischemic attack in the past 12 months. Selection of these participants was based on visual examination of a preexisting clinical MRI with the objective of sampling a distribution of white matter pathology. One participant did not complete the MoCA, so all analyses are based on the remaining 69 participants. Ethics approval was granted by the Hunter New England Human Research Ethics Committee (Ref: 10/03/17/5.04), and written informed consent was obtained from all participants. Participants completed three testing sessions. The first session included a large neuropsychological test battery and training on a task-switching paradigm. The second included EEG recording during task-switching and stop-signal tasks. The third involved the brain imaging protocol. The neuropsychological and experimental task results will be reported separately.

Table 1 presents summary data from the Wechsler Abbreviated Scale of Intelligence (normalized mean = 100, *SD* = 15; Wechsler, 1999), the digit span from the Wechsler Adult Intelligence Scale (WAIS-IV, normalized mean = 10, *SD* = 3; Wechsler, 2008), logical memory from the Wechsler Memory Scale (WMS-III, normalized mean = 10, *SD* = 3; Wechsler, 1997), and MoCA (Cronbach's alpha = 0.83; Nasreddine et al., 2005).[2] The participant group ranked high average on full-scale intelligence quotient (FSIQ) and working memory scores and low average on episodic memory, with a broad range in all measures.

A telephone screening procedure was used to assess suitability for inclusion in the current study, including contraindications to imaging. The interview also enquired about any current medical condition or health problem. Based on this information, more than half the participants (57%) were identified as having one or more vascular risk factors for which they were being medically treated (Table 1). Accurate medication information was not consistently available and is not reported here. The most common single risk factor was hypertension (64%), followed by high blood cholesterol and atrial fibrillation (14% each). Thirty-nine percent reported two or more risk factors. The most common pairs of risk factors were hypertension/cholesterol (47%), followed by diabetes/cholesterol (16%), and atrial fibrillation/obesity and atrial fibrillation/cholesterol (11% each). Of those with three or more risk factors, the most common were hypertension/atrial fibrillation with diabetes or obesity (25% each).

Table 1. *Summary Data of Participants*

Measure	Mean	*SD*	95% CI	Range
Age (years)	66.90	9.57	64.6–69.2	43–87
FSIQ	111.81	14.64	108.3–115.1	81–141
Working memory	10.70	2.96	10.01–11.41	3–19
Logical memory I	9.54	3.03	8.87–10.25	2–17
Logical memory II	9.06	2.97	8.38–9.75	1–16
MoCA score	25.96	3.09	25.2–26.7	17–30
Cerebral atrophy	26.42	4.77	25.4–27.6	15.42–36.74
(% ICV)	0.489	0.776	0.32–0.7	0.029–3.972
WMH (% ICV)	0.394	0.020	0.39–0.4	0.329–0.437
FA	0.585	0.031	0.58–0.59	0.534–0.662
MD	0.840	0.030	0.83–0.85	0.787–0.915
AxD	0.457	0.032	0.45–0.47	0.406–0.547
RaD				

Clinical profile	Yes	No
Vascular risk factors present	41 (59%) 25M/16F	28 (41%) 9M/19F
Hypertension	27 (39%) 15M/12F	
Hypercholesterolemia	22 (32%) 10M/12F	
Atrial fibrillation	11 (16%) 8M/3F	
Diabetes	6 (9%) 2M/4F	
Smoking	4 (6%) 4M/0F	
Obesity	6 (9%) 5M/1F	
Multiple vascular risk factors	27 (39%) 14M/13F	

Education	*N* (%)
Less than high school completion	21 (30%)
Completed high school	9 (13%)
TAFE/diploma	15 (22%)
Bachelor degree	19 (28%)
Postgraduate	5 (7%)

Note. *N* = 69 (34M/35F). M = male; F = female; MoCA = Montreal Cognitive Assessment; FSIQ = full-scale intelligence quotient; WMH = white matter hyperintensity; % ICV = percentage of intracranial volume; FA = fractional anisotropy; MD = mean diffusivity; AxD = axial diffusivity; RaD = radial diffusivity; TAFE = technical and further education.

Imaging Protocols

Imaging was completed on a 3T Siemens Verio scanner using a 32-channel head coil. T1-weighted images were acquired in the sagittal plane using ultrafast gradient echo 3D sequence (MPRAGE) with 1-mm isotropic voxel resolution (repetition time = 1,500 ms; echo time = 2.57 ms; inversion time = 900 ms; flip angle = 9°; slice thickness = 1 mm with no gap; TA = 3 min 29 s). A 3D fluid attenuated inversion recovery (FLAIR) sequence with 1-mm isotropic voxels was acquired in the sagittal plane using a phase-encoding acceleration factor of 2 (TR = 5,000 ms; TE = 395 ms; TI = 1,800 ms; 160 slices with slice thickness = 1 mm, TA = 5

1. The participants in the Jolly et al. (2013) study are a subset of those included in the present study. Jolly et al. (2013) excluded 10 participants because they had low MoCA scores and/or moderate WMH. They are included in this study because we focus on variability in MoCA.

2. The MoCA has only been validated for adults aged 55–85 years. While 10 participants fell outside this age range, an independent samples *t* test revealed that their mean MoCA score did not differ from the mean score for those participants whose age fell between this range, $t(67) = 0.503$, $p = .617$.

Table 2. *Correlations Between the Predictor Variables and the Outcome Variable Entered into the Stepwise Regression Model*

	Age	CA[a]	WMH[b]	FA	MD	AxD	RaD
MoCA	−.345*	−.452***	−.438***	.479***	−.504***	−.450***	−.517***
Age	–	.597***	.495***	−.505***	.604***	.573***	.603***
CA[a]	–	–	.471***	−.413***	.568***	.554***	.560**
WMH[b]	–	–	–	−.579***	.759***	.777***	.731***
FA	–	–	–	–	.882***	.732***	.931***
MD	–	–	–	–	–	.964***	.992***
AxD	–	–	–	–	–	–	.923***

Note. MoCA = Montreal Cognitive Assessment; CA = cerebral atrophy; WMH = white matter hyperintensity; % ICV = percentage of intracranial volume; FA = fractional anisotropy; MD = mean diffusivity; AxD = axial diffusivity; RaD = radial diffusivity.
[a]Calculated as a percentage of intracranial volume.
[b]Natural log of volume calculated as percentage of intracranial volume.
*$p < .05$. ***$p < .001$ after Bonferroni correction of $\alpha/7$; Pearson correlations, one-tailed.

min 52 s). Diffusion-weighted images were acquired in axial plane using a twice-refocused spin echo sequence with a phase-encoding acceleration factor of 3 (128 × 128 matrix; TR = 11,200 ms; TE = 111 ms; 55 slices with a slice thickness = 2.2 mm; TA = 13 min 6 s). Diffusion was measured in 64 noncollinear directions with a b value of 3,000 mm^2/s along with one nondiffusion weighted ($b = 0$) image. Measurements of blood flow pulsatility were quantified using a retrospectively cardiac-gated phase contrast flow quantification sequence (TR = 26.5 ms; TE = 6.9 ms; slice thickness = 5 mm; matrix 256 × 256). For the quantification of arterial flow, a single excitation with a velocity encoding value of 75 cm/s was used, and a section plane was implemented to intersect both the basilar artery as well as the cavernous portion of the internal carotid arteries at the level of the skull base (see Bateman, 2002).

Fiber Tracking

Whole-brain fiber tracking was performed using the MRtrix software package (Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/). Constrained spherical deconvolution (Tournier, Calamante, & Connelly, 2007) was used to model multiple fiber orientations, with a maximum harmonic order lmax = 8 being employed on these data. Probabilistic tracking was then performed using information from the derived fiber orientation distributions (Behrens et al., 2003). Whole-brain tracking was achieved by randomly seeding throughout a white matter mask based on segmentation of the T1-weighted image. Streamlines were discarded if they had a track length < 10 mm or extended beyond the white matter mask. A total of 8,000,000 streamlines were generated for each participant as it allowed us to utilize track density imaging (TDI; Calamante, Tournier, Jackson, & Connelly, 2010). Using TDI, we were able to reconstruct white matter tracts with increased resolution by taking advantage of long-range information contained in the diffusion MRI fiber tracks. We then used a threshold on the whole-brain TDI of 0.02% to remove any voxels that contained gray matter or suffered partial volume effects. The resulting voxels represented cerebral white matter (Jolly et al., 2013). Eighteen specific white matter tracts were also examined using the probabilistic white matter tract atlas from Johns Hopkins University (Hua et al., 2008). These 18 white matter tracts were aligned in standard space (EVE atlas) and resampled into participants' native space via a nonlinear registration procedure (FNIRT; Andersson, Jenkinson, & Smith, 2007), which is part of the FMRIB software library (Smith et al., 2004). Using the resampled tracts, we further isolated each tract by constraining them based on the results from the whole-brain tractography, and the resulting volume was used to calculate our tract-based DTI measures.

Quantifying Measures of White Matter and Arterial Pulsatility

WMH volume was determined for each participant in the FLAIR sequence by manually segmenting areas of hyperintense white matter and saving them as regions of interest. The total WMH volume was expressed as a percentage of intracranial volume. The WMH volumes ranged from 0.03% to 3.97%, and the distribution showed a strong positive skew ($N = 69$; skewness = 3.079; kurtosis = 10.203). Natural logarithm transform of WMH volumes ($N = 69$; skewness = 0.452; kurtosis = −0.536) were therefore used in the subsequent analyses. Cerebral atrophy was also calculated by taking total cerebral white matter and gray matter volume as a percentage of intracranial volume; this value was then subtracted from 100 so that larger values would indicate increased cerebral atrophy. Each participant's diffusion tensor was calculated using DTIfit within the FMRIB diffusion toolbox. Three eigenvectors that define the diffusion ellipsoid were calculated in each voxel from the diffusion tensor. These eigenvectors correspond to three eigenvalues, which represent the magnitude of diffusivity in the three principal directions. As such, voxelwise maps of white matter FA, MD, AxD, and RaD were derived. Mean FA, MD, AxD, and RaD were calculated for overall cerebral white matter as well as for each of the 18 separate white matter tracts. In order to calculate the arterial pulsatility index, a region of interest was placed around the basilar and carotid arteries. The blood flow was measured across this region, and the pulsatility index was calculated by dividing the difference between maximum and minimum flow by the mean flow across this region. This procedure is covered in greater detail elsewhere (Jolly et al., 2013).

Data Analysis

Pearson correlations, multiple linear regression, and mediation analyses were used to examine the effects of age and brain structural changes on global cognitive functioning, as measured by performance on the MoCA. All analyses were performed in SPSS v22 (IBM). Familywise error rate correction was used for correlations, as specified in relevant table legends. Mediation analyses were conducted using the PROCESS macro for SPSS (A. F. Hayes; http://www.processmacro.org).

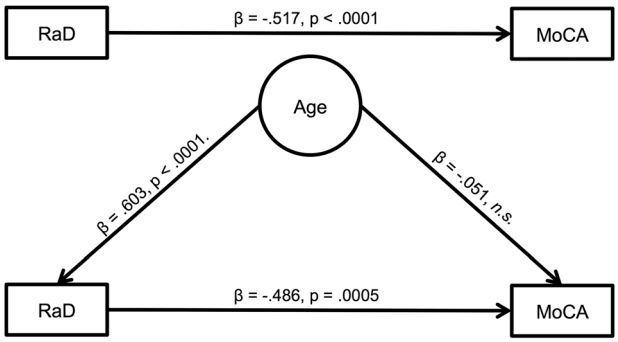

Figure 1. Direct relationship between total white matter radial diffusivity (RaD) and performance on the Montreal Cognitive Assessment (MoCA, top) and with age as a mediator (bottom). Beta values represent standardized coefficients, and direction of arrows reflects theoretically plausible relationships.

Results

Effects of Age and Brain Measures on Cognitive Performance

As seen in Table 2, all predictor measures were moderately to strongly correlated with MoCA scores and one another, $r = .345$–$.992$. Age and measures of total brain cerebral atrophy, white matter hyperintensity volume, FA, AxD, RaD were entered into a stepwise multiple linear regression to predict MoCA performance. A single model emerged, with RaD selected as the strongest sole predictor, accounting for ~27% of variance in MoCA scores, $F(1,67) = 24.4$, $p < .001$; $R^2 = .267$, $p < .001$. Neither age nor any of the other white matter measures were found to contribute to MoCA scores, over and above the effect of total white matter RaD. Since RaD was a stronger predictor of MoCA scores, compared to other structural brain measures, the remaining analyses were run using RaD only.

While RaD was selected as the strongest sole predictor of performance on the MoCA, simple linear regression showed that age was correlated with both white matter measures and MoCA scores (Table 2). As structural brain changes are more prominent with increasing age, we used mediation analysis to examine whether the effect of RaD on MoCA scores was mediated by age. While RaD was related to MoCA scores, $\beta = -.517$, $p < .001$ (Figure 1, top), and age, $\beta = .603$, $p < .001$ (Figure 1, bottom), the mediation model showed no significant effect of age on MoCA scores. Moreover, the direct effect of RaD on MoCA scores did not differ when accounting for age, $\beta = -.486$, $p < .001$. Thus, MoCA scores are lower for higher RaD and older age, and the mediation model that included both RaD and age showed that age does not mediate the relationship between white matter microstructure and cognitive performance. Rather, increasing RaD is associated with reduced MoCA scores, irrespective of age.

Global Cognitive Function and Tract-Specific Measures of White Matter Organization

We next examined whether regional RaD in any of the 18 white matter tracts was a stronger predictor of MoCA scores than global white matter RaD. Table 3 shows that RaD in most of the 18 tracts was moderately correlated with both MoCA scores and age, $r = .365$–$.519$. The only white matter tract to produce a stronger correlation with MoCA when compared to total brain white matter was the right uncinate fasciculus (UNC-r). In fact, in a stepwise multiple linear regression model with all 18 white matter tracts and total white matter as predictors of MoCA score, the only significant model had RaD in UNC-r explaining 27% of variance in MoCA scores, $F(1,67) = 24.7$, $p < .001$, $R^2 = .27$, $p < .001$. However, since all tracts were moderately to strongly correlated with total white matter RaD (Table 3), it is likely that UNC-r was selected as a result of a marginally stronger correlation strength than total white matter RaD (i.e., 0.519 vs. 0.517, respectively), rather than because it is functionally related to performance on the MoCA.

Table 3. *Correlations Between Radial Diffusivity in Individual White Matter Tracts with MoCA Scores, Age, and Global White Matter Radial Diffusivity*

RaD within specific white matter tract	MoCA	Age	Global WM RaD
ATR-left	−.463***	.483***	.848***
ATR-right	−.488***	.559***	.880***
CCFma	−.330*	.500***	.739***
CCFmi	−.450**	.626***	.889***
CST-left	−.379*	.456***	.796***
CST-right	−.465***	.514***	.762***
CgCin-left	−.446**	.609***	.844***
CgCin-right	−.440**	.541***	.839***
CgHi-left	−.290	.351*	.537***
CgHi-right	−.181	.089	.392**
IFO-left	−.459***	.602***	.943***
IFO-right	−.500***	.631***	.914***
ILF-left	−.411**	.599***	.908***
ILF-right	−.440**	.679***	.848***
SLF-left	−.480***	.497***	.947***
SLF-right	−.456***	.512***	.924***
UNC-left	−.503***	.596***	.887***
UNC-right	−.519***	.617***	.933***

Note. MoCA = Montreal cognitive assessment; RaD = radial diffusivity; WM = white matter; ATR = anterior thalamic radiation; CCFma = corpus callosum forceps major; CCFmi = corpus callosum forceps minor; CST = corticospinal tract; CgCin = cingulum of the cingulate gyrus; CgHi = cingulum of the hippocampus; IFO = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; UNC = uncinate fasciculus.
*$p < .05$. **$p < .01$. ***$p < .001$ after Bonferroni correction of $\alpha/18$.

To examine whether RaD in the UNC-r is a strong predictor of MoCA scores over and above overall brain changes in white matter RaD, we examined the partial correlation between RaD in UNC-r and MoCA scores when correcting for global white matter RaD. However, since UNC-r is a region that is also included in our measure of global white matter, we first removed the contribution of UNC-r on the calculation of global white matter. To do this, we created a separate control mask for UNC-r. The global white matter RaD voxelwise map was recalculated after applying this mask to exclude voxels belonging to UNC-r. As expected, the correlation between UNC-r and MoCA was no longer significant after controlling for variability in MoCA scores explained by global white matter RaD, $p > .14$. Therefore, RaD in global white matter, as opposed to any particular tract, is the most reliable predictor of global cognitive performance, as measured by the MoCA, and this relationship between white matter RaD and MoCA is not due to common variance related to age.

Presence of Cardiovascular Risk Factors

As the presence of cardiovascular risk factors has been associated with greater cognitive and structural brain changes in older adults (see introduction), we examined whether the relationship between white matter and MoCA is sensitive to factors that increase the risk

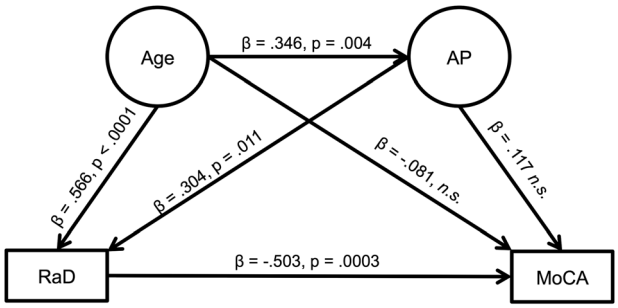

Figure 2. Relationship between RaD and MoCA with both age and arterial pulsatility (AP) as mediators. Beta values represent standardized coefficients, and direction of arrows reflects theoretically plausible relationships. *n.s.* = not significant.

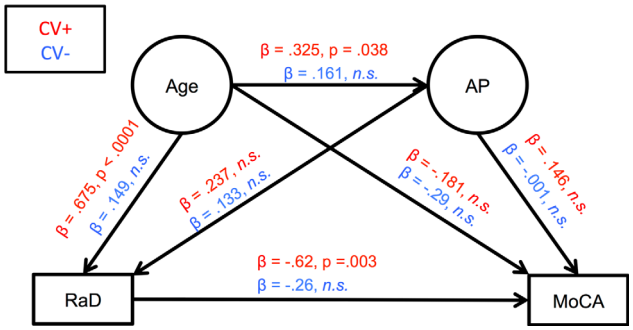

Figure 3. Relationship between RaD and MoCA with both age and arterial pulsatility (AP) as mediators, comparing CV-risk (red) and no-CV-risk (blue) groups. Beta values represent standardized coefficients, and direction of arrows reflects theoretically plausible relationships. *n.s.* = not significant.

of pathological changes in the white matter. Firstly, we examined whether the relationship between total white matter RaD and MoCA scores is mediated by variability in arterial pulsatility. Arterial pulsatility (AP) is a measure of the pulsatile quality of cerebral blood inflow that is considered an index of the overall health of the cerebrovascular system. An average measure of arterial pulsatility was derived across both internal carotid arteries and basilar artery. A previous study with a subset of this sample showed that greater arterial pulsatility is associated with reduced white matter microstructural organization, especially in the presence of cardiovascular risk factors (e.g., Jolly et al., 2013). It was therefore expected that arterial pulsatility may mediate the relationship between white matter RaD and MoCA performance. As shown in Figure 2, arterial pulsatility was positively related with both age and total brain white matter RaD, but not with cognitive performance. Moreover, like age, arterial pulsatility did not significantly mediate the effect of total white matter RaD on MoCA scores. Thus, although white matter microstructure is influenced by both age and arterial pulsatility, these variables do not mediate its effect on global cognitive abilities.

Secondly, as the majority of participants had at least one cardiovascular risk factor known to affect white matter integrity (e.g., hypertension, hypercholesterolemia) and the presence of cardiovascular risk factors was previously shown to impact the relationship between arterial pulsatility and white matter (Jolly et al., 2013), we examined whether the effect of RaD on MoCA varied as a function of the presence of cardiovascular risk factors. Participants were divided into two groups. The CV-risk group included participants who reported at least one cardiovascular risk factor ($n = 41$) and the no-CV-risk group included participants who reported no cardiovascular risk factor (no-CV-risk group: $n = 28$). On average, participants in the CV-risk group were significantly older ($M = 70.24$, $SD = 8.60$), scored significantly lower on the MoCA ($M = 25.07$, $SD = 3.36$) and had significantly greater white matter RaD ($M = 0.47$, $SD = 0.03$) than the no-CV-risk group ($M = 61.93$, $SD = 8.91$; $M = 27.25$, $SD = 2.10$; $M = 0.44$, $SD = 0.02$, respectively; independent samples t tests, all $ps < .003$).[3]

Figure 3 shows the mediation analysis run separately for the two groups. In the no-CV-risk group (CV-), standardized beta values were greatly reduced and there were no significant relationships between RaD, age, AP, and MoCA. In contrast, in the CV-risk group (CV+), most relationships shown in the whole group (Figure 2) were retained or strengthened.[4] Similar to the total group model, whole brain RaD was significantly associated with both MoCA and age, and there was no mediating effect of age or arterial pulsatility on the relationship between RaD and MoCA. Thus, in participants with a cardiovascular risk factor present, an increase in RaD was associated with a reduction in MoCA performance. These participants were also older and had more extensive RaD changes than participants with no cardiovascular risk factor, and are therefore likely candidates for pathological changes to white matter, which ultimately influences global cognitive functioning.

Discussion

In this study, we examined the relationship between age, white matter structure, and global cognitive performance in a sample of community-based, healthy older adults. Consistent with previous studies, we showed that increasing age was associated with changes in white matter microstructure (Salat et al., 2005; Sullivan et al., 2010; Vernooij et al., 2008) as well as reduced performance on the MoCA (Gluhm et al., 2013). Variability in white matter microstructure was a stronger predictor of MoCA performance than variability in white matter macrostructure (e.g., WMH) or whole brain atrophy. Moreover, radial diffusivity, a DTI measure that has been associated with myelination, showed the strongest relationship with MoCA scores, and this effect remained statistically significant even after controlling for variance associated with cerebral atrophy, WMH volume, and age. Thus, global cognitive performance is more sensitive to changes in white matter microstructure than to gross brain structure. These findings suggest that volumetric measures of brain structure may be too crude to detect early signs of global cognitive decline in otherwise healthy older adults.

3. Exploratory analyses looked at whether specific cardiovascular risk factors and/or combinations of risk factors replicated the pattern seen in the CV-risk group. No specific risk factor stood out more prominently.

4. The relationship between RaD and arterial pulsatility was weakened and failed to reach significance in the CV-risk group. This is surprising, as we have previously shown that higher arterial pulsatility was associated with increased RaD and that this association is strongest in participants with cardiovascular risk factors (Jolly et al., 2013). The current CV-risk group included the nine participants who had been excluded from Jolly et al. (2013) because they had low MoCA scores and/or extensive white matter disease. When we ran the mediation analysis on Jolly's smaller CV+ group, we produced highly similar results to those shown in Figure 3, except that the relationship between RaD and arterial pulsatility ($\beta = .502$, $p < .01$) was restored. This suggests that the impact of cardiovascular risk factors on brain white matter, arterial pulsatility, and cognitive performance is complex and requires further study.

In contrast, DTI-based measures of white matter microstructure appear to be sensitive to early indicators of global cognitive decline, even at a whole brain level. Although age, white matter microstructure, and global cognitive ability were intercorrelated, mediation analysis revealed no mediating effect of age on the relationship between MoCA and white matter RaD. Thus, although age is associated with a decline in both white matter microstructural organization and a decline in cognitive performance, the relationship between white matter microstructure and cognition cannot be explained by aging per se. Arterial pulsatility, a measure of the pulsatile properties of cerebrovascular blood inflow that has been previously shown to be linked to white matter hyperintensities (Bateman, 2002; Henry-Feugeas & Koskas, 2012) and changes in white matter microstructure (Jolly et al., 2013), also did not mediate the relationship between white matter microstructure and MoCA performance. The model in Figure 2 suggests that both age and arterial pulsatility impact white matter microstructural organization, which, in turn, affects global cognitive performance. However, as shown in Figure 3, the relationship between white matter microstructure and cognitive decline was only significant in the presence of cardiovascular risk factors, which have been associated with pathological changes in white matter. This conclusion is consistent with recent research showing that overall changes to cerebrovasculature affect the presentation of age-related changes to neural tissue (e.g., gray/white matter volume shrinkage, reduced arterial compliance, reduced cerebral blood flow; e.g., Fabiani et al., 2014, Katulska et al., 2014; Zimmerman et al., 2014).

The current findings suggest that reduced cognitive performance among older adults may be at least partially attributable to the emergence of white matter microstructural decline rather than to age itself. Therefore, at least some of the cognitive changes commonly reported in older adults are more likely to be related to the increased presence of cardiovascular risk factors with age. The present data suggest that one mechanism by which these cardiovascular risk factors may affect brain health and cognition is through their impact on white matter microstructural organization. This possible mediating role of cardiovascular health on age-related cognitive decline and associated brain changes is consistent with recent work by Chao et al. (2010), who showed that reduced cerebral perfusion was associated with an increased risk of progressing from mild cognitive impairment to dementia in older adults.

These findings have two important implications. Firstly, they show that poor performance on a global cognitive screening tool may prove to be a sensitive indicator of emerging white matter structural changes, especially in the presence of cardiovascular risk factors. Therefore, the inclusion of a simple cognitive screening tool, such as the MoCA, as part of routine cardiovascular risk assessments may provide important information about emerging damage to cerebral vasculature in older adults. Secondly, they highlight the need to control for the presence of cardiovascular risk factors when studying the effects of age on cognition. Currently, many cognitive aging studies do not systematically report the presence of cardiovascular risk factors in healthy older participants. Therefore, many of the cognitive differences between young and old age groups are likely to be accentuated by the increased presence of cardiovascular risk factors with increasing age. This may account for the increased interindividual variability often reported in older adults and discrepancies in the size and/or type of cognitive decline between studies of healthy aging. Our findings strongly advocate the need for studies of cognitive aging to control for the presence of cardiovascular risk factors and suggest that white matter changes may be a mediator of many typically reported cognitive effects of aging (see Bennett & Madden, 2014, for review).

In this study, we relied on the self-reported presence of cardiovascular risk factors and did not assess severity/duration of cardiovascular risk or the degree to which the condition was successfully treated. This is likely to have resulted in less clear distinction between the CV-risk present and no-CV-risk groups, especially as some participants in the latter group may in fact have emerging cardiovascular risk factors that have not yet been diagnosed. Despite this, we found large differences in the relationship between white matter microstructure and cognitive ability between the two groups. Future work is needed to systematically study the effects of different cardiovascular risk factors on cognition and differentiate between the effects of cardiovascular risk factors and the effects of medications used to reduce their impact on cardiovascular functioning (see also Footnote 3).

Finally, although in this study we used the MoCA score as an index of global cognitive functioning, the strongest relationship between MoCA performance and RaD was in the right uncinate fasciculus, a tract that supports frontotemporal white matter connections. This is consistent with evidence that changes to cerebral vasculature more strongly affect cognitive processes that rely on frontal networks. For instance, López-Olóriz et al. (2014) reported that increasing middle cerebral arterial pulsatility was linked to poorer executive function, attention, verbal fluency, memory, and processing speed. Knecht, Wersching, Lohmann, Berger, & Ringelstein (2009) reported that up to 11% of age-related changes in memory, executive function, attention, and verbal fluency were linked to systolic blood pressure. It is also consistent with clinical evidence that the MoCA is sensitive to frontal and frontotemporal dementia (Chertkow, Nasreddine, Philips, Litwin, & Whitehead, 2010; Freitas, Simões, Alves, Duro, & Santana, 2012; Miller, Banks, Léger, & Cummings, 2014), as well as MCI and Alzheimer's disease. It is possible to use the MoCA to extract measures related to specific cognitive domains (e.g., episodic memory, executive functioning, and attention; Dong et al., 2010; Nie et al., 2012; Wester, Westhoff, Kessels, & Egger, 2013). Future work is needed to examine whether these subscales are more sensitive to regional white matter changes than the global cognition score, and whether successful medical or lifestyle management of cardiovascular risk factors can ameliorate or delay any long-term effects on white matter microstructure (e.g., Zimmerman et al., 2014; see Bherer et al., 2013, for review).

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