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Age affects white matter microstructure and episodic memory across the older adult lifespan

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ABSTRACT

Diffusion imaging studies have observed age-related degradation of white matter that contributes to cognitive deficits separately in younger-old (ages 65–89) and oldest-old (ages 90+) adults. But it remains unclear whether these age effects are magnified in advanced age groups, which may reflect disease-related pathology. Here, we tested whether age-related differences in white matter microstructure followed linear or nonlinear patterns across the entire older adult lifespan (65–98 years), these patterns were influenced by oldest-old adults at increased risk of dementia (cognitive impairment no dementia, CIND), and they explained age effects on episodic memory. Results revealed nonlinear microstructure declines across fiber classes (medial temporal, callosal, association, projection and/or thalamic) that were largest for medial temporal fibers. These patterns remained after excluding oldest-old participants with CIND, indicating that aging of white matter microstructure cannot solely be explained by pathology associated with early cognitive impairment. Moreover, finding that the effect of age on episodic memory was mediated by medial temporal fiber microstructure suggests it is essential for facilitating memory-related neural signals across the older adult lifespan.

1. Introduction

White matter plays a crucial role in the transmission and coordination of neural impulses between gray matter regions (Salat, 2011). Significant and widespread white matter deterioration observed in normal aging results from demyelination, axonal shrinkage, decreased fiber density, and gliosis (Bartzokis, 2004; Bowley et al., 2010; Peters, 2019, 2002; Peters et al., 2010). Increases in the magnitude and extent of this white matter damage in advanced age (>90 years old) is thought to reflect pathologic processes associated with a higher prevalence of dementia and white matter disease in this age group (Corrada et al., 2010, 2008; Kawas et al., 2015; Wardlaw et al., 2015; Yang et al., 2013). However, few studies have assessed white matter aging across the older adult lifespan and whether these age effects are driven by individuals with or at risk for dementia through the tenth decade of life.

The microstructural composition of white matter can be assessed *in vivo* using diffusion tensor imaging (DTI), which measures the jitter (diffusion) of water molecules (Beaulieu, 2002; Jones, 2008; Mori and Zhang, 2006). In healthy white matter, microstructures such as axonal membranes and myelin restrict the diffusion of water, which causes the primary diffusion direction to occur along the length of these structures rather than perpendicular to them. DTI measures these diffusion properties to provide estimates of the degree of restricted diffusion (fractional anisotropy; FA) and the average rate of diffusion parallel (axial diffusivity; AD) or perpendicular (radial diffusivity; RD) to the primary diffusion direction (Beaulieu, 2002; Jones, 2008; Jones et al., 2013; Mori and Zhang, 2006).

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DTI studies in healthy younger-old adults without dementia (i.e., ages 60–89) report a relatively consistent pattern of linear age-related decreases in FA and increases in both AD and RD, with the magnitude of these effects varying by fiber class. That is, the largest age-related differences are seen in the fornix (de Groot et al., 2016; Kochunov et al., 2007; Lövdé et al., 2013), a medial temporal region that connects the hippocampus to cortical regions, and the genu of the corpus callosum (Barrick et al., 2010; Lövdé et al., 2013), a callosal region that connects frontal cortex in the left and right hemispheres. Large age effects are also observed within association fibers that connect cortical gray matter regions within the same hemisphere (e.g., external capsule)(Cox et al., 2016; Lövdé et al., 2013). However, projection and thalamic fibers that connect cortical gray matter regions to the spinal cord (e.g., corona radiata) and thalamus (e.g., thalamic radiations), respectively, show minimal age effects (Cox et al., 2016; de Groot et al., 2016; Lövdé et al., 2013). These regional variations have also been observed in DTI aging studies across the lifespan (Bendlin et al., 2010; Cox et al., 2016; Giorgio et al., 2010; Hsu et al., 2010; Hugenschmidt et al., 2008; Isaac Tseng et al., 2020; Kennedy and Raz, 2009; Kochunov et al., 2012; Lebel et al., 2012; Malykhin et al., 2011; Michielse et al., 2010; Mooij et al., 2018; Stadlbauer et al., 2008a, 2008b; Westlye et al., 2010; Xie et al., 2016).

Of note, very few DTI studies of healthy older adults without dementia have included a sizeable number of individuals beyond 90 years of age (c.f., Beck et al., 2021; de Groot et al., 2016), where the high prevalence of dementia-related cognitive impairment and white matter disease may magnify the effect of aging on microstructure (Yang et al., 2013). We focused on nonagenarians in a previous study ($n = 94$; Bennett et al., 2017), finding the largest age-related microstructure differences (decreased FA, increased diffusivity) in medial temporal (fornix) and callosal (splenium) regions, comparable to what is seen in younger-old adults, except that it was the splenium and not genu of the corpus callosum that was affected within the oldest-old. Importantly, these age-microstructure relationships did not differ between cognitively normal oldest-old adults and those diagnosed with cognitive impairment no dementia (CIND). However, because this earlier study did not include a younger-old comparison group, it remains unknown whether age is linearly related to white matter microstructure across the full extent of the older adult lifespan or whether there are nonlinear age effects on microstructure that may reflect disproportionate increases in normal age or disease-related pathology in advanced age.

To address this gap, the current study recruited 108 individuals across the older adult lifespan (65–98 years), including nonagenarians from The 90+ Study (Kawas and Corrada, 2006), who underwent diffusion imaging and completed an episodic memory task. Our first aim tested whether the effect of age on white matter microstructure was better explained by linear or nonlinear models. We hypothesized that more extensive white matter damage in advanced age would be seen as nonlinear effects of age on white matter microstructure, with the largest age-related differences in medial temporal and callosal fiber classes. Our second aim tested whether these relationships were affected by oldest-old adults diagnosed with CIND. We hypothesized that the age-microstructure relationships would not differ after excluding oldest-old adults diagnosed with CIND, consistent with our previous work in nonagenarians (Bennett et al., 2017), suggesting that these microstructure measures are capturing normal aging processes rather than pathology associated with early cognitive impairment. Our third aim was to assess the functional relevance of white matter aging, focusing on relationships between medial temporal microstructure and episodic memory given our interest in early cognitive impairment (Bastin and Salmon, 2014; Jahn, 2013).

2. Method

2.1. Participants

We recruited a total of 110 older adults (65–98 years, 64 female). Seventy-nine younger-old adults (65–92 years, 46 female) from the Riverside community voluntarily responded to online and print advertisements. Thirty-one oldest-old adults (90–98 years, 18 female) were a subset selected from current participants in The 90+ Study, a longitudinal study of aging and dementia in the oldest-old (see Kawas and Corrada, 2006 for additional details), who had not previously received a diagnosis of dementia. All participants were screened for conditions that would prevent them from being able to enter the magnetic resonance imaging (MRI) scanner (e.g., having ferrous metal implants). Younger-old participants were further screened for self-reporting major neurologic (e.g., mild cognitive impairment, dementia, stroke), mental health (e.g., depression, schizophrenia), or medical (e.g., diabetes, emphysema) conditions. Oldest-old participants underwent a thorough neurologic, physical, and neuropsychological evaluation by trained examiners. One younger-old adult with whole-brain microstructure measures >4 standard deviations from the mean of their age group and 1 oldest-old adult with a cortical mass that covered large portions of parietal white matter were excluded from all analyses. Demographic and neuropsychological data for the final sample of 108 participants can be found in Table 1.

This study was conducted in compliance with the Institutional Review Boards for the University of California, Riverside and Irvine. Each participant provided informed consent and was compensated for their participation.

2.2. Cognitive status

For the oldest-old only, diagnoses of cognitively normal ($n = 20$) and cognitive impairment no dementia (CIND; $n = 9$) were made by a trained clinician based on cognitive or functional losses that were not of sufficient severity to meet the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for dementia (American Psychiatric Association, 1994; Graham et al., 1997). The clinical evaluation was missing for 1 oldest-old participant who was included in the CIND group because they scored 25 on the Mini Mental State Examination (MMSE; Folstein et al., 1975). These data are presented in Table 1.

General cognitive status was assessed in the younger-old sample using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), although no participant was excluded based on these scores because of our interest in early cognitive impairment.

2.3. Episodic memory task

Episodic memory was assessed using the Rey Auditory Verbal Learning Task (RAVLT; Rey, 1941). Participants listened to and recalled a list of 15 words (List A) across 5 separate trials followed by a second list of 15 words (List B) for a single trial. Delayed recall was measured as the number of words correctly recalled from List A after 30 minutes. Finally, participants listened to a list of words containing all items from Lists A and B ($n = 30$) and words that are phonetically or semantically similar ($n = 20$) and were asked to indicate whether a word was previously presented on List A. Recognition memory performance was measured as the difference between the number of words correctly (Hits) and incorrectly (False Alarms) classified as being present on List A. Recognition data was not obtained from 1 younger-old participant due to time constraints.

Table 1
Demographic and neuropsychological data.

Mean ± SD	Whole sample	Younger-old	Oldest-old	t/χ^2 (p)
N	108	78	30	na
Age, years	79.1 ± 10.3	73.7 ± 6.3	93.2 ± 1.9	**16.7 (<0.001)**
N female (%)	63 (58.3%)	45 (57.7%)	18 (60%)	0.05 (0.83)
N CIND (%)	-	-	10 (33%)	na
N Hispanic (%)	7 (6%)	6 (8%)	1 (3%)	0.68 (0.41)
Education, years	15.4 ± 3.0	15.5 ± 3.0	15.2 ± 3.1	0.64 (0.52)
MoCA	-	26.4 ± 2.4	-	na
MMSE	-	-	25.7 ± 2.9	na
RAVLT Delayed Recall	7.1 ± 3.4	7.7 ± 3.3	5.5 ± 3.4	**3.1 (0.002)**
RAVLT Recognition	8.1 ± 6.4	10.0 ± 4.2	3.0 ± 8.0	**5.9 (<0.001)**

Notes: Demographic and neuropsychological test data are presented as mean ± standard deviation (SD), separately for younger- and oldest-old adults. Significant group differences at $p < 0.05$ are indicated by bolded t or χ^2 (% female, N Hispanic) statistics. MoCA, montreal cognitive assessment, MMSE, mini-mental state exam, RAVLT, rey auditory verbal learning task, CIND, cognitive impairment no dementia, na, not applicable.

2.4. Structural image acquisition

Structural imaging data were acquired using a 3T Siemens Prisma MRI scanner fitted with a 32-channel head coil at the University of California, Riverside (younger-old sample) or the University of California, Irvine (oldest-old sample).

A single high-resolution T1-weighted image (magnetization-prepared rapid gradient-echo sequence, MPRAGE) was acquired with the following parameters: Echo time (TE)/repetition time (TR) = 2.72/2400 ms, field of view (FOV) = 256 × 256 × 208 mm, matrix size of 320 × 320 × 260, voxel size = 0.8 mm^3, a Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) acceleration factor of 2, 208 axial slices, scan time = 6:28.

Whole brain diffusion-weighted MRI data were acquired with a diffusion-weighted single-shot spin-echo, echo planar imaging (EPI) sequence with the following parameters: TE/TR = 102/3500 ms, FOV = 212 × 182 mm^2, matrix size of 128 × 110, voxel size = 1.7 mm^3, multiband factor = 4, 64 slices with no gap, scan time = 16:12. Bipolar diffusion-weighting gradients were applied in 64 directions with b values of 1500 s/mm^2 and 3000 s/mm^2 with 3 $b = 0$ images. The multiband factor used here was based on the Human Connectome Project (HCP) protocol (Glasser et al., 2016; Harms et al., 2018), with any potential reductions in the signal to noise ratio offset by increasing the voxel size.

2.5. Diffusion imaging data

2.5.1. Preprocessing

For each participant, diffusion data were preprocessed using AFNI (Analysis of Functional NeuroImages; Cox, 1996) to remove non–brain tissue and generate a whole-brain mask and FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) to correct for head movement and eddy-current induced distortions. FSL's DTIFIT was then used to estimate a single diffusion tensor for each voxel, using data from both b values, with the whole-brain mask limiting tensor fitting to brain tissue. The output included voxel-wise images for FA, AD ($\lambda 1$), and RD ($\lambda 2 + \lambda 3/2$).

Diffusion data from the full sample (78 younger-old, 30 oldest-old) is reported here without correction for EPI distortions. In a subset of primarily younger-old participants (78 younger-old, 8 oldest-old), a second diffusion sequence was acquired with phase-encoding directions of opposite polarity, which allowed for EPI distortion correction (FSL's TOPUP). To assess the impact of this preprocessing step, microstructure measures (FA, AD, and RD) were separately extracted from both the non–EPI-corrected and EPI-corrected data within a white matter mask (the mean FA skeleton) for this subset of participants. We then computed a traditional Pearson R value between these datasets, separately for each diffusion metric. Importantly, we observed strong correlations between the non–EPI-corrected and EPI-corrected data for each metric ($R \geq 0.88$, $p \leq 0.0001$), providing confidence that the results reported here would be comparable to those found with EPI-corrected data.

2.5.2. Region segmentation

We used Tract Based Spatial Statistics (TBSS; Smith et al., 2006) to identify the locally maximal FA values within white matter common to all participants (mean FA skeleton). Each individual's FA map was first nonlinearly aligned to the FMRIB58_FA template in Montreal Neurological Institute 152 standard space. The mean of all aligned FA volumes was then used to create an average white matter skeleton specific to this sample, using a threshold of 0.2 to exclude voxels that contained minimal white matter. The aligned and thresholded FA images from each participant were projected onto the mean FA skeleton. The mean skeleton was then multiplied by a binarized standard white matter atlas to limit analyses to regions contained within the JHU ICBM-DTI-81 white matter labels atlas in FSL (Mori et al., 2008). Finally, the TBSS non–FA pipeline was used to register each participant's AD and RD images to the mean FA skeleton in FMRIB58_FA 1mm^3 space.

This approach resulted in 15 skeletonized standard regions of interest (excluding brainstem and cerebellar regions) from the following fiber classes: Medial temporal (fornix body, fornix cres, hippocampal cingulum, uncinate fasciculus), corpus callosum (genu, body, splenium), association (superior cingulum, external capsule, inferior sagittal stratum, superior longitudinal and fronto-occipital fasciculi) and projection and/or thalamic (corona radiata, internal capsule, posterior thalamic radiations). These classes were based on anatomic standards (Wakana et al., 2004; Wycoco et al., 2013).

2.5.3. Microstructure measures

Measures of white matter microstructure were extracted from standard regions of interest for each participant by binarizing each skeletonized standard region and multiplying it by the corresponding microstructure map (FA, AD, RD). Mean microstructure values were converted to z-scores for each region and then averaged across regions within the same fiber class (medial temporal, callosal, association, projection and/or thalamic) for each participant. Analyses of individual regions are provided in Supplemental Table 1.

2.5.4. Controlling for hyperintense white matter

To assess the potential effect of white matter hyperintensities, we replicated all analyses using microstructure measures that were limited to normal appearing white matter within the white matter

skeleton. A white matter mask that excludes hyperintense tissue was generated on each participant's MPRAGE image via FSL's FAST (Zhang et al., 2001), which classifies white matter hyperintensities as either grey matter or cerebrospinal fluid due to their low-intensity values (Melazzini et al., 2021). We then thresholded each participant's white matter mask (partial volume estimate >0.5), aligned it to diffusion space using a linear boundary-based registration with 12° of freedom, and multiplied it by the voxel-wise images for each diffusion metric. These microstructure maps were input into the TBSS non–FA pipeline to register each participant's diffusion images to the mean FA skeleton in FMRIB58_FA 1mm^3 space. Normal appearing white matter microstructure measures were then extracted from the standard regions of interest for each participant and averaged across regions within the same fiber class as discussed above.

2.6. Statistical analyses

Analyses were conducted using a combination of SPSS Version 26, Prism Version 9, and R-Studio Version 1.1.442. All analyses controlled for sex and education.

To assess age-related differences in white matter microstructure, linear regressions were conducted between chronological age and white matter microstructure, separately for each fiber class (medial temporal, callosal, association, projection and/or thalamic) and diffusion metric (FA, AD, RD). Significant effects (coefficients of determination, R^2) survived Bonferroni correction for comparisons across 4 fiber classes, p-values (ps) < 0.013.

To test whether a nonlinear model better explained the relationship between chronological age and white matter microstructure, linear regressions were conducted between chronological age squared and white matter microstructure, separately for each fiber class and diffusion metric. We then compared model fit between linear (age) and nonlinear (age and age squared) models, with better fit indicated by smaller corrected Akaike Information Criterion (AICc) and significant likelihood ratio tests (Akaike, 1974; Spiess and Neumeyer, 2010; Wagenmakers and Farrell, 2004). To assess the regional specificity of these age effects, we also used likelihood ratio tests to compare model fit between regions and microstructure measures best fit by a linear or nonlinear model. To assess the impact of pathology associated with early cognitive impairment or white matter hyperintensities, we then repeated the linear versus nonlinear regression analyses and model comparisons after excluding oldest-old adults with CIND or using microstructure measures from normal appearing white matter (i.e., excluding hyperintense white matter).

Finally, we sought to assess the functional relevance of age-related differences in white matter microstructure by testing whether medial temporal microstructure mediated the effect of age on episodic memory performance. First, separate linear regressions related chronological age or age squared to each memory measure (recognition, delayed recall) to medial temporal microstructure, separately for each diffusion metric (Bonferroni corrected for comparisons across 3 microstructure measures, p < 0.017). As above, model fit was assess using AICc values and likelihood ratio tests. Next, for each medial temporal diffusion metric that exhibited significant relationships to memory performance, separate mediation analyses conducted using the PROCESS macro for SPSS (Hayes and Rockwood, 2017) assessed the indirect effect of age (linear relationships) or age squared (nonlinear relationships) on memory performance via white matter microstructure using a 95% confidence interval (CI) based on bootstrapping with 5000 replacements. CIs that did not include zero were considered to be statistically significant. These analyses were then repeated to the explore the potential mediating effect of other fiber classes.

Table 2
Linear and nonlinear model comparisons of age effects on all white matter.

	Whole sample (linear/nonlinear)		
Fiber class	FA	AD	RD
Medial temporal			
R^2	**0.38/0.39**	0.04/0.03	**0.47/0.48**
AICc	-89.58/-**94.88**	-**48.67**/-49.96	-104.9/-**107.7**
χ^2 (p)	**8.05 (0.005)**	0.90 (0.34)	**5.45 (0.02)**
Association			
R^2	**0.19/0.20**	**0.38/0.37**	**0.34/0.35**
AICc	-44.95/-**47.50**	-**88.26**/-89.48	-61.66/-**62.99**
χ^2 (p)	**5.11 (0.02)**	1.01 (0.32)	**3.77 (0.05)**
Callosal			
R^2	**0.14/0.15**	**0.22/0.22**	**0.25/0.25**
AICc	-26.28/-**28.50**	-**56.59**/-57.04	-38.73/-**40.25**
χ^2 (p)	**4.28 (0.04)**	1.82 (0.18)	**3.96 (0.05)**
Projection/thalamic			
R^2	**0.17/0.18**	**0.37/0.36**	**0.31/0.31**
AICc	-28.90/-**29.24**	-**78.90**/-77.63	-44.55/-**44.86**
χ^2 (p)	**5.40 (0.02)**	0.94 (0.33)	2.01 (0.16)

Notes: Analyses testing the effect of age on white matter microstructure, controlling for sex and education, are presented separately for each diffusion metric (fractional anisotropy, FA; axial diffusivity, AD; radial diffusivity, RD) and fiber class. Coefficients of determination (R^2) are presented from regression analyses between age (linear) or age squared (nonlinear). Significant effects Bonferroni corrected at p < 0.013 are bolded. Akaike Information Criterion (AICc) values and χ^2 (p) values from likelihood ratio tests are reported for regression models of age (linear) or age and age and age squared (nonlinear). Significantly better fits (significant χ^2, smaller AICc) for the nonlinear relative to the linear model are bolded.

3. Results

3.1. Linear effects of age on white matter microstructure

First, we conducted linear regressions to assess the effect of chronological age on white matter microstructure (Bonferroni corrected, p < 0.013), separately for each fiber class and diffusion metric. Results revealed that older age was linearly associated with decreased FA and increased AD and RD in each fiber class, R^2 > 0.14, $ps \leq 0.001$, except for AD in the medial temporal fiber class, $p = 0.048$ (Table 2 and Fig. 1; see Supplemental Table 1 for individual regions). Importantly, this pattern of results remained unchanged when the linear regressions were repeated after excluding oldest-old adults with CIND (Table 3) and when using microstructure measures from normal appearing white matter (Table 4).

3.2. Nonlinear effects of age on white matter microstructure

Next, we conducted linear regressions to assess the effect of chronological age squared on white matter microstructure, separately for each fiber class and diffusion metric. Results revealed that older age was nonlinearly associated with decreased FA and increased AD and RD in each fiber class, R^2 > 0.15, $ps \leq 0.001$, except for AD in the medial temporal fiber class, $p = 0.054$ (Table 2 and Fig. 1; see Supplemental Table 1 for individual regions). A similar pattern of results was observed when the linear regressions were repeated after excluding oldest-old adults with CIND (Table 3) and when using microstructure measures from normal appearing white matter (Table 4).

A comparison of the linear and nonlinear models for each fiber class revealed smaller AICc values for nonlinear models and significant likelihood ratio tests, χ^2 > 3.77, ps < 0.05, for medial temporal (FA, RD), association (FA, RD), callosal (FA, RD), and projection and/or thalamic (FA) fiber classes (Table 2 and Fig. 1), indicating that age-related differences in white matter microstruc-

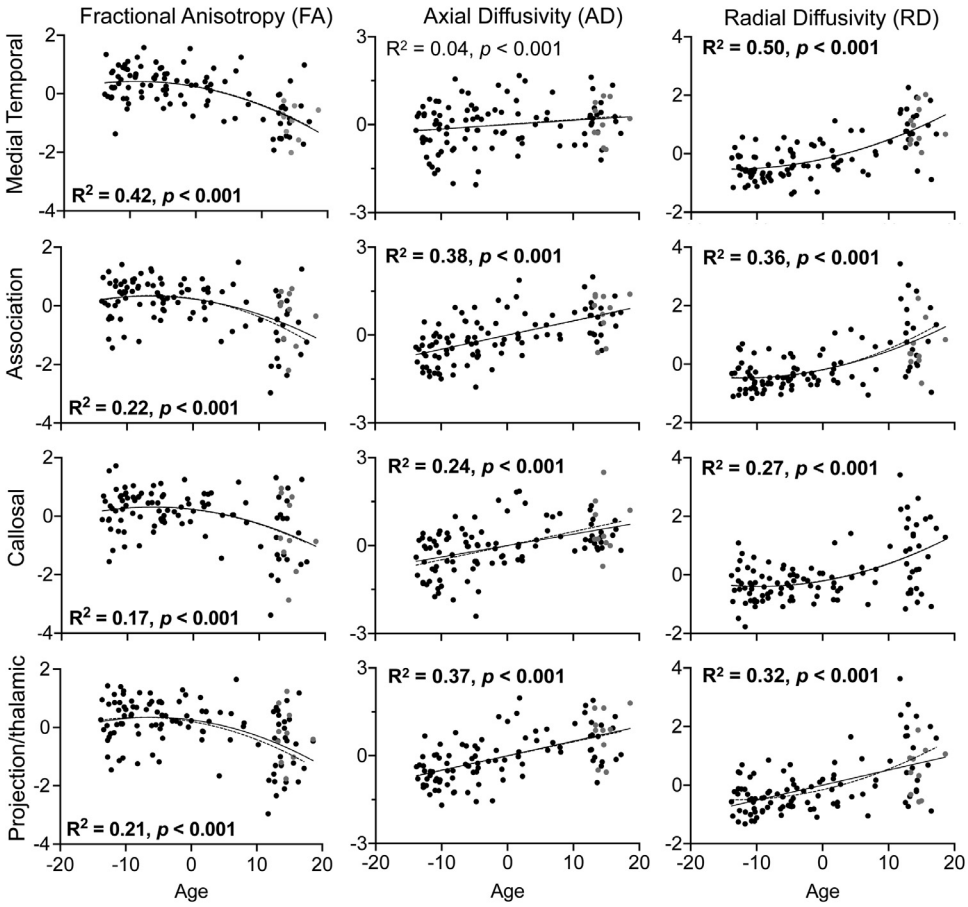

Fig. 1. Scatterplots display relationships between age and white matter microstructure (FA, AD, RD) across the sample, separately for each fiber class (medial temporal, callosal, association, projection/thalamic). The regression line and coefficients of determination (R^2) reflect whether the linear (straight line) or nonlinear (curved line) analysis were a better fit (smaller AICc, significant likelihood ratio test). All relationships remained the same after excluding oldest-old adults diagnosed with cognitive impairment no dementia (CIND; gray circles, dotted lines), except that projection/thalamic FA/RD were better fit by a nonlinear model.

ture from these regions were magnified in advanced age. In contrast, smaller AICc values for linear models and non–significant likelihood ratio tests for AD in all fiber classes and for RD in the projection and/or thalamic fiber class, *ps* > 0.16, suggests that the AD metric and RD in this fiber class were better captured by linear age-related differences in white matter microstructure across the older adult lifespan. Importantly, this pattern of results remained unchanged when analyses were repeated after excluding oldest-old adults with CIND, except that now a nonlinear model better explained age-related differences for projection and/or thalamic RD (Table 3 and Fig. 1). Moreover, when using microstructure measures from normal appearing white matter, the nonlinear model remained a significantly better fit for medial temporal and association FA, and callosal RD (Table 4).

3.3. Regional specificity of age effects on white matter microstructure

For each region and diffusion metric better fit by a nonlinear or linear model, we then assessed whether the relationship with age differed across fiber classes using separate likelihood ratio tests. For FA, results revealed that a nonlinear model was a significantly better fit for the medial temporal fiber class relative to all 3 other fiber classes, $\chi^2 > 47.71$, *ps* < 0.001, for the association and projection and/or thalamic fiber classes relative to callosal fiber class, $\chi^2 > 19.03$, *ps* < 0.001, and for the association relative to projection and/or thalamic fiber class, $\chi^2 = 16.18$, $p < 0.001$. Similarly, for RD, results revealed that a nonlinear model was a significantly better fit for the medial temporal fiber class relative to the association and callosal fiber classes, $\chi^2 > 45.51$, *ps* < 0.001, and for the association relative to the callosal fiber class, $\chi^2 = 22.71$, $p < 0.001$. For AD, results further revealed that the linear model was a significantly better fit for all other fiber classes relative to medial temporal fiber class, $\chi^2 > 7.19$, *ps* < 0.001, for the association relative to callosal and projection and/or thalamic fiber classes, $\chi^2 > 9.98$, *ps* < 0.001, and for the projection and/or thalamic relative to callosal fiber class, $\chi^2 = 21.82$, $p < 0.001$.

3.4. Medial temporal microstructure mediates age-memory relationships

Having established a wide-spread effect of age on white matter microstructure, we then sought to assess its functional relevance by testing whether it mediated the effect of age on episodic memory performance, focusing on medial temporal microstructure. First, separate linear regressions were conducted between chronological age and each memory measure, controlling for sex and education. As expected, results revealed that older age was significantly related to worse recognition, $\beta = -0.43$, $p < 0.001$, and recall, $\beta = -0.28$, $p = 0.001$, performance (Fig. 2). Smaller AICc values were observed for the nonlinear relative to linear model for recognition (linear = 369.6, nonlinear = 367.6) and delayed recall (linear = 238.5, nonlinear = 237.8), and the nonlinear model was a significantly better fit for explaining age-related differences in recognition memory, $\chi^2 = 4.56$, $p = 0.033$.

Table 3
Linear and nonlinear model comparisons on all white matter without CIND.

	Without CIND (linear/nonlinear)		
Fiber class	FA	AD	RD
Medial temporal			
R^2	**0.31/0.32**	0.04/0.04	**0.42/0.43**
AICc	-79.11/**-83.45**	**-41.86**/-40.39	-96.96/**-99.43**
χ^2 (p)	**6.91 (0.009)**	0.82 (0.37)	**4.72 (0.03)**
Association			
R^2	**0.20/0.21**	**0.34/0.34**	**0.34/0.35**
AICc	-43.09/**-47.85**	**-81.58**/-82.42	-57.03/**-59.87**
χ^2 (p)	**7.93 (0.005)**	1.32 (0.25)	**5.85 (0.02)**
Callosal			
R^2	**0.13/0.13**	**0.20/0.19**	**0.22/0.25**
AICc	-33.08/**-34.78**	-55.12/**-55.40**	-41.38/**-42.44**
χ^2 (p)	**4.68 (0.03)**	2.89 (0.09)	**3.93 (0.05)**
Projection/thalamic			
R^2	**0.19/0.20**	**0.33/0.32**	**0.31/0.32**
AICc	-27.79/**-30.12**	**-74.19**/-73.73	-40.40/**-41.25**
χ^2 (p)	**5.44 (0.02)**	1.54 (0.21)	**3.86 (0.05)**

Notes: Analyses testing the effect of age on white matter microstructure, controlling for sex and education, are presented separately for each diffusion metric (fractional anisotropy, FA; axial diffusivity, AD; radial diffusivity, RD) and fiber class. Coefficients of determination (R^2) are presented from regression analyses between age (linear) or age squared (nonlinear). Significant effects Bonferroni corrected at $p < 0.013$ are bolded. Akaike Information Criterion (AICc) values and χ^2 (p) values from likelihood ratio tests are reported for regression models of age (linear) or age and age and age squared (nonlinear). Significantly better fits (significant χ^2, smaller AICc) for the nonlinear relative to the linear model are bolded.

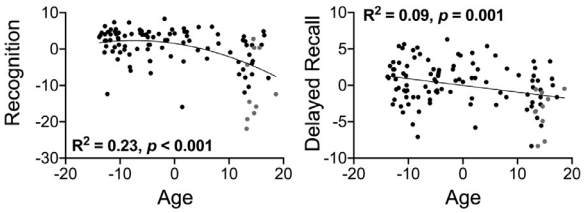

Fig. 2. Scatterplots show significant linear (straight) or nonlinear (curved) regression lines and coefficients of determination (R^2) from the regression analyses across the entire sample between age and RAVLT recognition (left) and delayed recall (right), independent of sex and education. Oldest-old adults diagnosed with cognitive impairment no dementia (CIND) is displayed as gray circles.

Next, linear regressions were conducted between medial temporal microstructure and each memory measure (Bonferroni corrected, $p < 0.017$). For recognition, results revealed that better performance was significantly related to higher medial temporal FA, $\beta = 0.36$, $p < 0.001$, and lower RD, $\beta = -0.31$, $p < 0.001$, with a nonlinear model better explaining the relationship between recognition and medial temporal FA (linear = -55.62, nonlinear = -58.90, $\chi^2 = 4.27$, $p = 0.039$). For delayed recall, results revealed that better performance was significantly related to higher medial temporal FA, $\beta = 0.26$, $p = 0.008$, and AD, $\beta = 0.23$, $p = 0.017$. Smaller AICc values were observed for the nonlinear relative to linear model for medial temporal FA (linear = -46.55, nonlinear = -46.94), but the nonlinear model did not significantly better explain age-related differences in delayed recall, $p = 0.137$.

Finally, for each medial temporal diffusion metric that was significantly related to memory performance, we tested whether white matter microstructure mediated the linear (recall) or nonlinear (recognition) effect of age on that memory measure (Fig. 3 and Table 5). Results revealed that only AD in the medial temporal fiber class significantly mediated the linear relationship between age and delayed recall. Of note, a similar pattern of results was

Table 4
Linear and nonlinear model comparisons on the white matter-masked data.

	Whole sample (linear/nonlinear)		
Fiber class	FA	AD	RD
Medial temporal			
R^2	**0.42/0.43**	0.00/0.00	**0.28/0.29**
AICc	-95.65/**-103.50**	**-52.65**/-53.53	**-100.8**/-102.8
χ^2 (p)	**10.84** (<0.001)	3.24 (0.07)	0.23 (0.63)
Association			
R^2	**0.22/0.23**	**0.27/0.27**	**0.31/0.32**
AICc	-51.93/**-55.02**	**-84.15**/-83.49	**-57.18**/-57.91
χ^2 (p)	**5.69 (0.02)**	1.59 (0.21)	3.15 (0.08)
Callosal			
R^2	**0.20/0.20**	**0.09/0.09**	**0.21/0.21**
AICc	**-65.05**/-64.90	**-77.66**/-76.30	-34.53/**-36.31**
χ^2 (p)	2.14 (0.14)	0.84 (0.36)	**4.26 (0.04)**
Projection/thalamic			
R^2	**0.21/0.21**	**0.26/0.26**	**0.26/0.27**
AICc	**-35.02**/-35.71	**-69.71**/-69.36	**-39.42**/-38.57
χ^2 (p)	3.07 (0.08)	1.91 (0.17)	1.42 (0.23)

Notes: Analyses testing the effect of age on white matter microstructure, controlling for sex and education, are presented separately for each diffusion metric (fractional anisotropy, FA; axial diffusivity, AD; radial diffusivity, RD) and fiber class. Coefficients of determination (R^2) are presented from regression analyses between age (linear) or age squared (nonlinear). Significant effects Bonferroni corrected at $p < 0.013$ are bolded. Akaike Information Criterion (AICc) values and χ^2 (p) values from likelihood ratio tests are reported for regression models of age (linear) or age and age and age squared (nonlinear). Significantly better fits (significant χ^2, smaller AICc) for the nonlinear relative to the linear model are bolded.

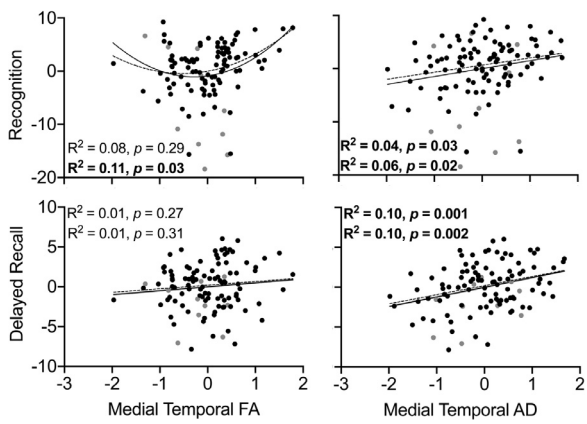

Fig. 3. Scatterplots display significant (bolded) relationships between medial temporal fractional anisotropy (FA; left) or axial diffusivity (AD; right) and memory performance (recognition, recall), independent of age, sex, and education, as well as age squared (medial temporal FA vs. recognition). Separate linear regression lines and coefficients of determination (R^2) are shown for analyses conducted with (solid black line; top statistics) or without (black dotted line; bottom statistics) oldest-old adults diagnosed with cognitive impairment no dementia (CIND; gray circles).

observed after excluding oldest-old adults with CIND, except that medial temporal FA also mediated the nonlinear relationship between age and recognition memory. Similar results were observed when analyses using microstructure measures from normal appearing white matter and effects were comparable in the left and right hemispheres. When these analyses were conducted for the other fiber classes, there was no significant evidence of mediation for recall, suggesting these effects are specific to the medial temporal white matter, but there was an additional mediation effect of projection and/or thalamic FA on recognition after excluding oldest-old adults with CIND (data not shown).

Table 5
Mediating effects of medial temporal microstructure on episodic memory.

Mediator	Whole sample Indirect effect (LLCI, ULCI)	Without CIND Indirect effect (LLCI, ULCI)
Delayed recall		
Medial temporal FA	-0.024 (-0.064, 0.013)	-0.019 (-0.060, 0.016)
Medial temporal AD	**0.018 (0.001, 0.038)**	**0.018 (0.0009, 0.039)**
Recognition		
Medial temporal FA	-0.002 (-0.006, 0.002)	**-0.004 (-0.008, -0.0001)**
Medial temporal RD	0.0005 (-0.003, 0.006)	-0.0009 (-0.004, 0.002)

Notes: For each memory measure that was independently related to both age and medial temporal matter microstructure, indirect effects and their corresponding lower-level (LL) and upper-level (UL) confidence intervals (CI) are presented for analyses testing whether microstructure mediated the effect of age (delayed recall) or age squared (recognition) on that memory measure (controlling for sex and education), conducted with (left) or without (right) oldest-old adults diagnosed with cognitive impairment no dementia (CIND). Significant effects are indicated by confidence intervals that did not contain zero (bolded).

3.5. Effect of age on white matter hyperintensity volume

For descriptive purposes, we conducted a linear regression to assess the effect of chronological age on white matter hyperintensity volume, calculated as the difference in the number of voxels between the original all-FA skeleton and the all-FA skeleton limited to normal appearing white matter for each participant. As expected, results revealed that older age was associated with higher hyperintensity volume, $R^2 = 0.11$, $p = 0.004$ (younger-old: 166.95 ± 282.08; oldest-old: 825.00 ± 1847.35, including 2 participants with hyperintense volumes >4 standard deviations above the mean).

4. Discussion

The current study examined how age affects white matter microstructure of 4 major fiber classes within an older adult lifespan sample that included a sizeable number of nonagenarians from The 90+ Study. Results revealed significant nonlinear age-related declines in microstructure (decreased FA, increased RD) of the medial temporal, association, callosal, and projection and/or thalamic fiber classes. Importantly, these effects of age on microstructure remained significant even after excluding oldest-old adults diagnosed with CIND and when limiting analyses to microstructure measures from normal appearing (i.e., excluding white matter hyperintensities), suggesting that they primarily reflect normal aging processes rather than pathology associated with early cognitive impairment or white matter disease. When assessing the functional relevance of these declines, we found that medial temporal microstructure mediated the effects of age on episodic memory performance. Together, these findings indicate widespread age-related degradation of white matter that is exacerbated across the older adult lifespan, with disruption of neural signals in medial temporal white matter contributing to age-related memory differences.

To our knowledge, this is the first study to assess the linearity of white matter microstructure declines in older adults spanning the seventh through tenth decades of life. Finding that age effects on microstructure were better explained by nonlinear, compared to linear, models suggests that age-related degradation of white matter is accelerated in advanced age. This pattern of results extends what was previously known about white matter aging in younger-old adults (between ages 55–90) who primarily exhibit linear age-related declines in white matter microstructure (Barrick et al., 2010; de Groot et al., 2016; Kochunov et al., 2007; Lövdé et al., 2013). Although nonlinear effects of age on microstructure had previously been reported in lifespan studies that assess individuals ranging from childhood or young adulthood up to age 90 (Bendlin et al., 2010; Cox et al., 2016; Hsu et al., 2008; Kennedy and Raz, 2009; Lebel et al., 2012; Malykhin et al., 2011; Mooij et al., 2018; Westlye et al., 2010), white matter aging across the older adult lifespan is likely driven by different neural substrates. For example, whereas early life stages are characterized by development of white matter (e.g., increased myelination and axonal sprouting that continues through midlife; Walhovd et al., 2014; Yeatman et al., 2014), older adults, and particularly oldest-old adults, are vulnerable to neurodegenerative processes. Relative to younger-old adults, cognitively normal oldest-old adults have a high prevalence of white matter disease among numerous other subclinical neural pathologies (e.g., neurofibrillary tangles, microinfarcts, amyloidosis)(Jacobs et al., 2018; Kawas et al., 2015; Pereira et al., 2019), which would contribute to decreases in white matter microstructure (decreased FA, increased AD and/or RD). Of note, these pathologic processes may not have been fully captured by previous white matter aging studies that focused only on younger-old adults, which may explain the difference between their observations of linear age effects and the current findings of nonlinear age effects.

Importantly, the nonlinear effects of age on white matter microstructure remained significant after excluding oldest-old adults diagnosed with CIND, consistent with our prior work within nonagenarians (Bennett et al., 2017). Because these individuals are at a heightened risk of developing dementia (Peltz et al., 2011), we speculated that the presence of dementia-related pathology (e.g., amyloid plaques, neurofibrillary tangles; Arfanakis et al., 2020) may contribute to larger age effects on white matter in advanced age. Our finding of similar patterns of results after excluding participants with CIND supports the notion that white matter in oldest-old adults may be more vulnerable to processes associated with normal aging of white matter (e.g., demyelination, myelin ballooning; Peters, 2002).

This interpretation is further supported by nonlinear age effects in medial temporal FA, association FA, and callosal RD that remained significant when using microstructure measures that were limited to normal appearing white matter. Given that oldest-old participants were only excluded if they met criteria for dementia, it remains possible that other chronic conditions contribute to the observed widespread nonlinear effects of age on white matter microstructure. For example, age-related cardiovascular diseases (including hypertension and diabetes) and small vessel disease (Wardlaw et al., 2015) are known to negatively affect white matter (e.g., gross and microscopic infarcts, arteriolosclerosis; Arfanakis et al., 2020). However, by excluding participants with CIND and white matter hyperintensities, our control analyses demonstrate that aging of white matter that is more pronounced toward the end of the older adult lifespan is not solely due to pathology associated with early cognitive impairment or white matter hyperintensities. This conclusion is further strengthened by our observation that the nonlinear age effects on white matter microstructure did not vary after excluding after excluding 13 participants who meet the definition for “superager” (i.e., 80+ years, RAVLT delayed recall ≥ 9; data not shown; (Harrison et al., 2012; Rogalski et al., 2019).

Comparisons between fiber classes revealed that the magnitude of nonlinear age effects were largest for the medial temporal fiber class and smallest for the callosal fiber class (FA, RD), which was reflective of the individual regions within each class (see Supplemental Table 1). For example, there were larger effects for the fornix compared to the body and splenium of the corpus callosum (callosal), sagittal stratum (association), and internal capsule or corona radiata (projection). Studies of younger-old adults have similarly found that medial temporal microstructure is especially vulnerable to aging (Bennett and Stark, 2016; Hoagey et al., 2019;

Rieckmann et al., 2016; Yang et al., 2016), consistent with studies of medial temporal (hippocampal) gray matter microstructure and volume (Langnes et al., 2020; Raz et al., 2010; Venkatesh et al., 2020). Aging of medial temporal microstructure has been attributed to these regions containing smaller diameter axons and lower oligodendrocyte-to-axon ratios (Stebbins and Murphy, 2009), as well as being relatively late to myelinate (Bartzokis, 2004). Of note, because this result was not driven by oldest-old adults diagnosed with CIND, who presumably have dementia-related pathology accumulating in medial temporal white matter (Braak and Braak, 1997), it further supports the notion that vulnerability of medial temporal white matter is primarily attributed to the aforementioned normal aging processes. In contrast, relatively smaller age effects for the callosal fiber class suggest that these fibers are somewhat preserved across the older adult lifespan. Whereas the genu of the corpus callosum is noted for being more vulnerable to aging in younger-old adults (Bennett et al., 2010; Burzynska et al., 2010), it is minimally affected in oldest-old adults (Bennett et al., 2017), and the opposite pattern holds true for the splenium of the corpus callosum. The interaction of these age and regional differences likely results in the net minimal effect of aging on callosal fibers.

We further found that age indirectly affected memory performance via medial temporal white matter microstructure, even after excluding oldest-old adults diagnosed with CIND. Independent of age, higher medial temporal FA predicted better memory recognition performance, and higher AD predicted better recognition and delayed recall performance, with additional effects observed between recognition and projection and/or thalamic FA. These findings replicate and extend previous studies that found relationships between medial temporal white matter microstructure (i.e., fornix, uncinate fasciculus, hippocampal cingulum) and episodic memory in younger-old or lifespan samples (Bennett et al., 2015; Bennett and Stark, 2016; Foster et al., 2019; Ly et al., 2016; Metzler-Baddeley et al., 2019) and suggest that these memory processes are primarily dependent on the medial temporal lobe (Yonelinas et al., 2010). They also provide compelling support for the cortical disconnection hypothesis of cognitive aging (Bartzokis, 2004; Bennett and Madden, 2014; O'Sullivan et al., 2001), which proposes that degradation of white matter interferes with the transmission of neural signals and ultimately contributes to cognitive dysfunction in older adults. Of note, whereas previous studies in cognitively normal younger-old adults find that aging uniquely affects free recall (Bennett et al., 2015; Stark et al., 2013; Toner et al., 2009; Yassa et al., 2011), our observation of age-related declines in both recognition and free recall are more consistent with previous reports in cognitively impaired younger-old (Chen and Chang, 2016; Clark et al., 2012; Stark et al., 2013). This may indicate that impairments in both forms of memory and their medial temporal substrates are characteristic of normal cognition in advanced age, although this claim would benefit from future studies that can further test the specificity of these results by comparing multiple forms of cognition.

The present study is strengthened by our large sample with age ranges spanning the older adult lifespan, examination of diffusion imaging data across the whole brain, and assessment of the functional relevance of white matter declines in aging to episodic memory. A potential limitation is that our younger-old and oldest-old adults were recruited and tested at separate locations, which presents a potential confound with the age effects of interest. Importantly, however, we used identical MRI scanners and imaging sequences across sites, which has previously been shown to attenuate inter-site variability (Venkatraman et al., 2015). Although TBSS performs superior registration of major white matter pathways across participants, which is especially important in advanced aging populations that experience significant atrophy, it can lack anatomic specificity for regions with multiple fiber populations (e.g., superior cingulum) or in close proximity to the ventricles (e.g., fornix)(Bach et al., 2014). To avoid overstating the tract-based specificity of our results, TBSS was primarily used to identify robust and common white matter pathways that were then subject to a standard atlas and collapsed across fiber class. Finally, we did not perform clinical assessments for CIND within the younger-old cohort, although general cognitive status for these participants was assessed using the MoCA. Our interpretations will be strengthened by future studies replicating and extending the current effects of age and cognitive impairment on white matter microstructure across the older adult lifespan, especially those focusing on older adults with direct measures of known dementia-related pathology, including amyloid-beta and tau neurofibrillary tangles (Janelidze et al., 2020; Thijssen et al., 2020).

In closing, this study revealed widespread age-related differences in white matter microstructure between the seventh and tenth decades of life that were better fit by a nonlinear relationship, with the largest effects seen in the medial temporal fiber class, and that were not solely driven by oldest-old adults with cognitive impairment or by white matter hyperintensities. Moreover, age-related differences in the microstructure of medial temporal fibers mediated the effect of age on both delayed recall and recognition memory performance. Furthering our understanding of white matter aging and its impact on episodic memory in this way is timely given global trends of growth in the older adult population, and in particular of oldest-old adults (He and Muenchrath, 2011).

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Declarations of competing interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.06.021.

CRediT authorship contribution statement

Jenna L. Merenstein: Data curation, Writing – original draft, Visualization, Investigation, Formal analysis. **María M. Corrada:** Funding acquisition, Writing – review & editing. **Claudia H. Kawas:** Funding acquisition, Writing – review & editing. **Ilana J. Bennett:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – review & editing.

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