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An MRI Investigation of Neurocognitive Aging in the Oldest-Old

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Dedication

This dissertation is dedicated to the memory of my late maternal grandmother, Beverly Jean Williams, who always believed in my academic success and supported my endeavors to chase my dreams. Her passing occurred early into older adulthood and inspired me to conduct this research on how the brain contributes to us living healthier, longer lives.

ABSTRACT OF THE DISSERTATION

An MRI Investigation of Neurocognitive Aging in the Oldest-Old

by

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The number of individuals experiencing age-related cognitive decline will increase as the population of older adults continues to rise, with the fastest growing segment being oldest-old adults aged 85+ years. These cognitive deficits can be at least partly attributed to age-related declines in the underlying neural substrates (e.g., white matter microstructure), which can be measured in living individuals using magnetic resonance imaging (MRI). However, MRI studies examining the association between cognitive and brain aging across the older adult lifespan rarely use samples that extend into advanced age. To address this limitation, this dissertation studied neurocognitive aging within oldest-old adults using diffusion MRI and integrative review methodologies. Chapter 1 used traditional single tensor diffusion imaging to examine the linearity of age-related declines in white matter microstructure across 108 adults ages 65-98 years. Results indicated accelerated brain-wide white matter microstructure degradation into advanced age, with medial temporal white matter microstructure mediating the negative effect of age on episodic memory performance. Chapter 2 used more advanced multicompartment diffusion imaging to assess relations between white matter

microstructure and associative learning performance within a subset of 22 oldest-old adults from Chapter 1. Results indicated preserved associative learning abilities into the 10th decade of life that were supported by better microstructure of white matter connections between the prefrontal cortex and dorsal striatum. Findings from Chapters 1 and 2 were independent of diagnoses of cognitive impairment no dementia in oldest-old adults, suggesting that they were not driven by advanced age-related cognitive dysfunction. Finally, Chapter 3 examined whether these findings align with those from other MRI studies of oldest-old adults as well as predictions of select neurocognitive aging theories. Despite there being some continuity across the older adult lifespan, results indicated that older adults also have unique cognitive and neural profiles during the eighth through tenth decades of life. Together, this collection of findings (1) supports the notion that advanced age affects white matter microstructure and in turn cognitive ability and (2) highlights the importance of considering oldest-old adults in modern neurocognitive aging research.

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General Introduction

The number of individuals over age 65 will double over the next 30 years (United Nations, 2010), which will result in an increase in the number of individuals suffering from Alzheimer's disease and related dementias. But declines in cognitive abilities are also a hallmark feature of normal aging and are evident even in older adults without clinical evidence of cognitive impairment or dementia. Across cognitive domains, some of the largest deficits are seen for learning and memory processes (Park and Reuter-Lorenz, 2009), which have been attributed to age-related declines in brain structure and function using magnetic resonance imaging (MRI) techniques (Hartel and Buckner, 2006; Tromp et al., 2015; Young et al., 2020). These types of MRI studies are critical for identifying neural biomarkers that can be used for the early detection of cognitive impairment and predicting the trajectory of age-related cognitive decline.

Despite representing the fastest growing segment of the population (He and Muenchrath, 2011; Houser, A., Fox-Grage, W., and Ujvari, 2012), however, oldest-old aged ~80+ years are rarely included in MRI studies examining neurocognitive aging. Of the handful of MRI studies using samples extending into advanced age, most have focused on the disease-related neural changes seen in oldest-old adults with cognitive impairment or dementia (Corrada et al., 2010, 2008; Yang et al., 2013). Even less is known about oldest-old adults without dementia, 50% of whom have no evidence of brain pathologies (Kawas et al., 2015). Consequently, much remains to be discovered about neurocognitive aging in this advanced age group, which is a primary goal of this dissertation.

One neural substrate contributing to cognitive performance across the lifespan is the microstructural composition of white matter tissue, which is comprised of fiber bundles of myelinated axons that connect gray matter regions (e.g., neuronal cell bodies, dendrites). Healthy white matter contributes to efficient neurotransmission by propagating action potentials between neurons in a rapid and synchronous manner, which ultimately benefits cognitive functioning (Salat, 2011). In older adults, however, the cortical disconnection hypothesis proposes that age-related degradation of white matter interferes with the transmission of neural signals between brain regions, thereby resulting in cognitive dysfunction (Bartzokis, 2004; O'Sullivan et al., 2001). Nonetheless, white matter is relatively less studied than its gray matter counterpart, despite constituting ~50% of neural tissue (Fields, 2010) and being relatively more affected by age (e.g., Giorgio et al., 2010). As such, additional studies examining white matter microstructure and its relation to cognition are necessary to obtain a more holistic understanding of neurocognitive aging, especially within the oldest-old.

One of the specific aims of this dissertation is to further our understanding of neurocognitive aging in the oldest-old using diffusion-weighted imaging (DWI), which is an MRI technique that assesses the microstructural composition of white matter *in vivo.* In healthy white matter, the movement of water is restricted by microstructures like axonal membranes and myelin, which causes water to move freely along the length of a white matter pathway rather than perpendicular to it (Beaulieu, 2002; Jones, 2008; Jones et al., 2013; Mori and Zhang, 2006). DWI capitalizes on these properties to provide estimates of the rate and degree of restricted water movement along these white matter

pathways (Beaulieu, 2002; Jones, 2008; Mori and Zhang, 2006). Here, DWI was used to assess the linearity of age-related differences in white matter microstructure and its relation to episodic memory across the entire older adult lifespan (Chapter 1) as well as the contribution of white matter microstructure to associative learning performance within oldest-old adults (Chapter 2). Chapter 3 then integrates these findings with those reported by other MRI studies using advanced age groups and examines whether they would be predicted by modern theories of neurocognitive aging.

Chapter 1 assessed white matter aging across the brain within older adults ages 65-98 years, including oldest-old adults diagnosed with cognitive impairment no dementia. This study used traditional single tensor diffusion imaging (DTI), which fits a single tensor (stick) to each voxel to estimate the degree of restricted water diffusion or the rate of diffusion (Beaulieu, 2002; Jones, 2008; Jones et al., 2013; Mori and Zhang, 2006). In contrast to earlier DTI work examining age effects on white matter microstructure separately within younger-old (ages 65-80 years) or oldest-old (ages 80+ years) adults, a simultaneous investigation of these effects across both age groups may reveal more accelerated effects of normal aging in the oldest-old. Larger age effects on microstructure in the 10^{th} decade of life may also reflect the higher prevalence of cognitive impairment and dementia-related pathologies in advanced age. The chapter concludes by testing whether white matter microstructure predicts episodic memory performance, which was measured using a standard neuropsychological list learning task. Results are expected to demonstrate that advanced age has widespread and nonlinear

effects on white matter microstructure that accounts for episodic memory declines across the older adult lifespan.

Chapter 2 used a more advanced multicompartment diffusion imaging approach called Neurite Orientation Density and Dispersion Index (NODDI; Zhang et al., 2012) to assess the relation between white matter microstructure and performance on a laboratory-based measure of associative learning within a subset of 22 oldest-old adults from Chapter 1. Associative learning refers to the ability to extract predictable relationships among events in the environment, such as meeting new people or learning a new technology (Lieberman, 2000; Seger, 1994). Studies using NODDI within younger-old adults have previously demonstrated greater sensitivity to cognitive performance than traditional DTI (Radhakrishnan et al., 2020; Venkatesh et al., 2020), which may be due to the way that NODDI provides separate estimates of intracellular (restricted), extracellular (dispersed), and free (unrestricted) water diffusion within a single voxel. This study focuses on the fornix and internal capsule as white matter regions of interest because they connect gray matter regions shown to be active while younger age groups engage in associative learning (i.e., hippocampus, striatum, prefrontal cortex). In support of the notion that these regions are critical to associative learning across the lifespan, results are expected to demonstrate that oldest-old adults with lower microstructure in these regions show minimal evidence of associative learning, whereas individuals with higher microstructure have better associative learning performance.

Chapter 3 examines how other MRI studies in oldest-old adults have contributed to our understanding of brain and cognitive aging in the oldest-old by reviewing their

findings within the context several theories of neurocognitive aging. Because these theoretical predictions were derived from cohorts of younger-old adults, it is possible that they may not generalize into advanced age, particularly because oldest-old adults have more advanced brain aging and an increased prevalence of cognitive impairment and dementia-related pathologies. It is also possible that cognitively normal oldest-old adults represent a unique group of individuals who are aging more successfully than the general older adult population. This integrative literature review is expected to demonstrate that older adults exhibit different cognitive and neural profiles during the eighth through 10th decades of life. If so, modern neurocognitive aging theories may need to be modified to account for the heterogeneity in brain and cognitive aging that occurs in the oldest-old.

Taken together, this body of work lays the groundwork for future MRI studies examining advanced neurocognitive aging by furthering our understanding about the aging of white matter microstructure and its utility in predicting memory and learning performance in oldest-old adults. The findings from this dissertation, along with those from future MRI studies in the oldest-old, will ultimately inform effective interventions designed to delay and prevent normal age-related cognitive decline. Moreover, given the increased prevalence of cognitive impairment in this advanced age group (Brookmeyer et al., 2017; Corrada et al., 2008), this collection of studies will also contribute to the early identification of older individuals at risk for Alzheimer's disease and related dementias.

Chapter 1: Age Affects White Matter Microstructure and Episodic Memory Across the Older Adult Lifespan

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/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.

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 pathological 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).

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; Lövdén 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; Lövdén 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; Lövdén 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; Lövdén 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).

Method

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 neurological (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 neurological, 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 one 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.

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, 4th edition criteria for dementia (American Psychiatric Association, 1994; Graham et al., 1997). The clinical evaluation was missing for one 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.

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 five 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 one younger-old participant due to time constraints.

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 x 320 x 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 = 1.7mm^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.

Diffusion Imaging Data

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.

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/thalamic

(corona radiata, internal capsule, posterior thalamic radiations). These classes were based on anatomical standards (Wakana et al., 2004; Wycoco et al., 2013).

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/thalamic) for each participant. Analyses of individual regions are provided in Supplementary Table 1 (Appendix A).

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 degrees 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.

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/thalamic) and diffusion metric (FA, AD, RD). Significant effects (coefficients of determination, R^2) survived Bonferroni correction for comparisons across four fiber classes, *p*-values (*p*s) < 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 three 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.

Results

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 Figure 1; see Supplementary 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).

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 Figure 1; see Supplementary 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, $\chi^2 > 3.77$, $ps < 0.05$, for medial temporal (FA, RD), association (FA, RD), callosal (FA, RD), and projection/thalamic (FA) fiber classes (Table 2 and Figure 1), indicating that age-related differences in white matter microstructure 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/thalamic fiber class, *p*s > 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/thalamic RD (Table 3 and Figure 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).

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 three other fiber classes, $\chi^2 > 47.71$, *p*s < 0.001, for the association and projection/thalamic fiber classes relative to callosal fiber class, $\chi^2 > 19.03$, *p*s < 0.001, and for the association relative to projection/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, $\chi^2 > 45.51$, *p*s < 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, $\chi^2 > 7.19$, *p*s < 0.001, for the association

relative to callosal and projection/thalamic fiber classes, $\chi^2 > 9.98$, ps < 0.001, and for the projection/thalamic relative to callosal fiber class, $\chi^2 = 21.82$, $p < 0.001$.

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 (Figure 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, $\chi^2 = 4.56$, $p = 0.033$.

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 (Figure 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 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/thalamic FA on recognition after excluding oldest-old adults with CIND (data not shown).

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 two participants with hyperintense volumes > 4 standard deviations above the mean).

Discussion

The current study examined how age affects white matter microstructure of four 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/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 white matter (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; Lövdén 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/RD). Of note, these pathological 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 Supplementary 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; A. C. 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/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 anatomical 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).

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)**

Note. 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.

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)

Note. 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 AIC) for the nonlinear relative to the linear model are bolded.

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)**

Note. 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 AIC) for the nonlinear relative to the linear model are bolded.

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)

Note. 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 AIC) for the nonlinear relative to the linear model are bolded.

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

	Whole Sample	Without CIND
Mediator	Indirect effect (LLCI, ULCI)	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)

Note. 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).

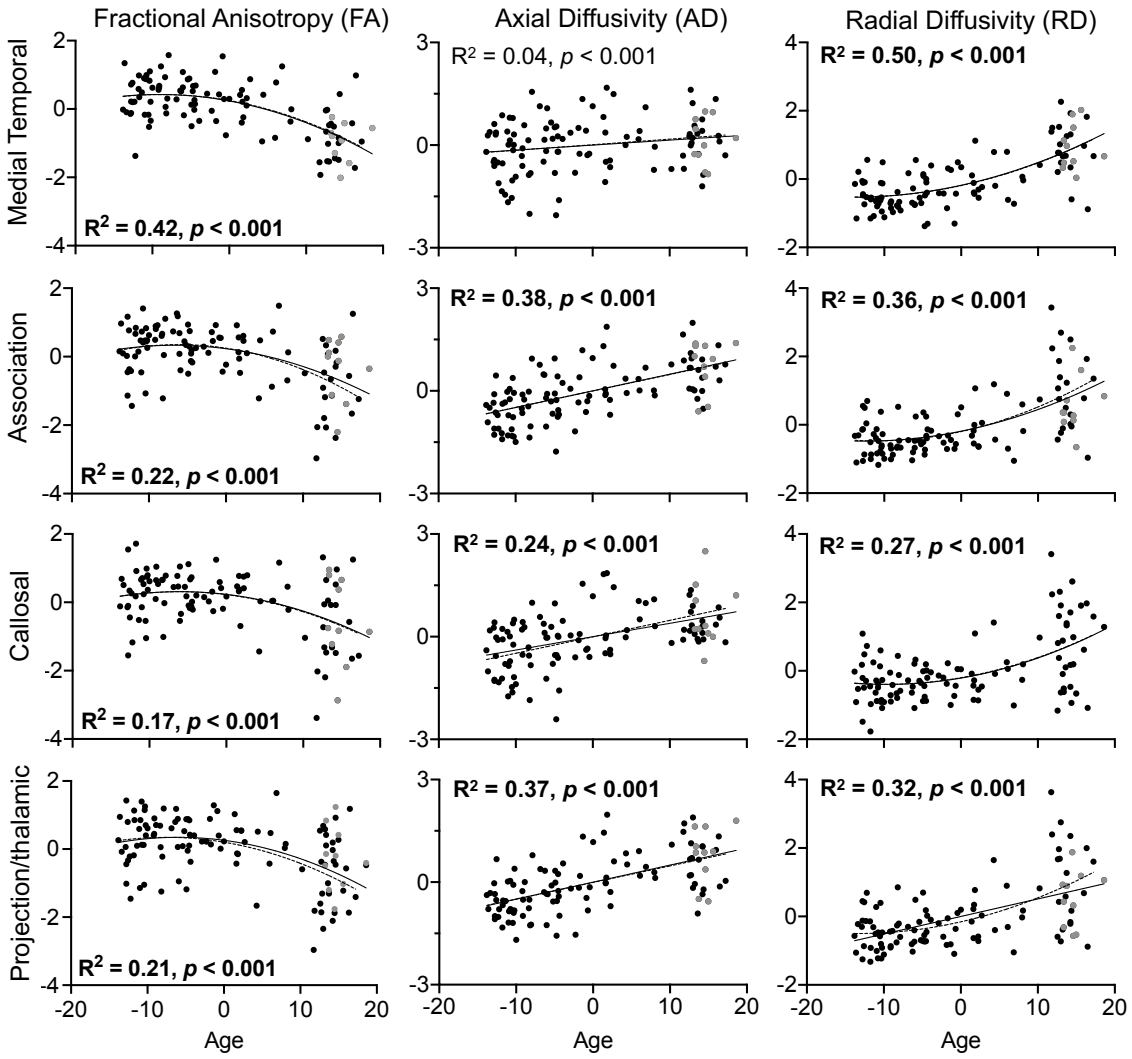

Figure 1. Scatterplots display relationships between age and white matter microstructure (FA, AD, RD) across the sample, separately for each fiber class (medial temporal, callosal, association, projection/thalamic). The regression line and coefficients of determination (R^2) reflect whether the linear (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.

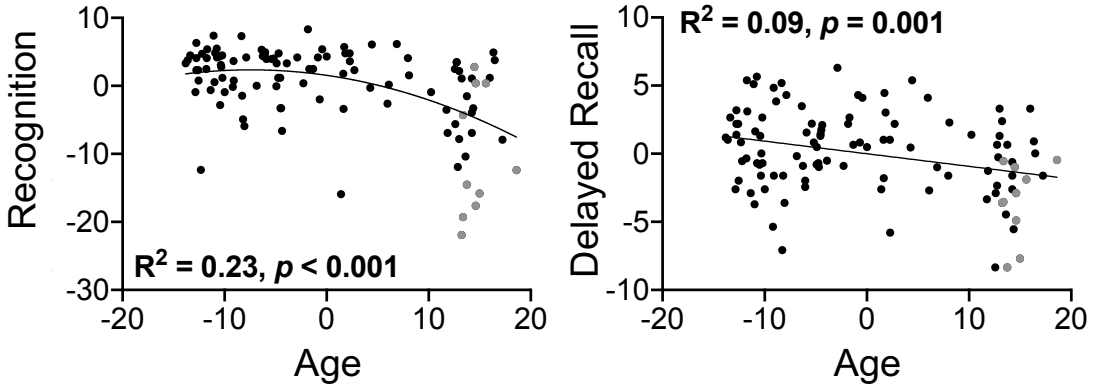

Figure 2. Scatterplots show significant linear (straight) or nonlinear (curved) regression lines and coefficients of determination (R^2) from the regression analyses across the entire sample between age and RAVLT recognition (left) and delayed recall (right), independent of sex and education. Oldest-old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

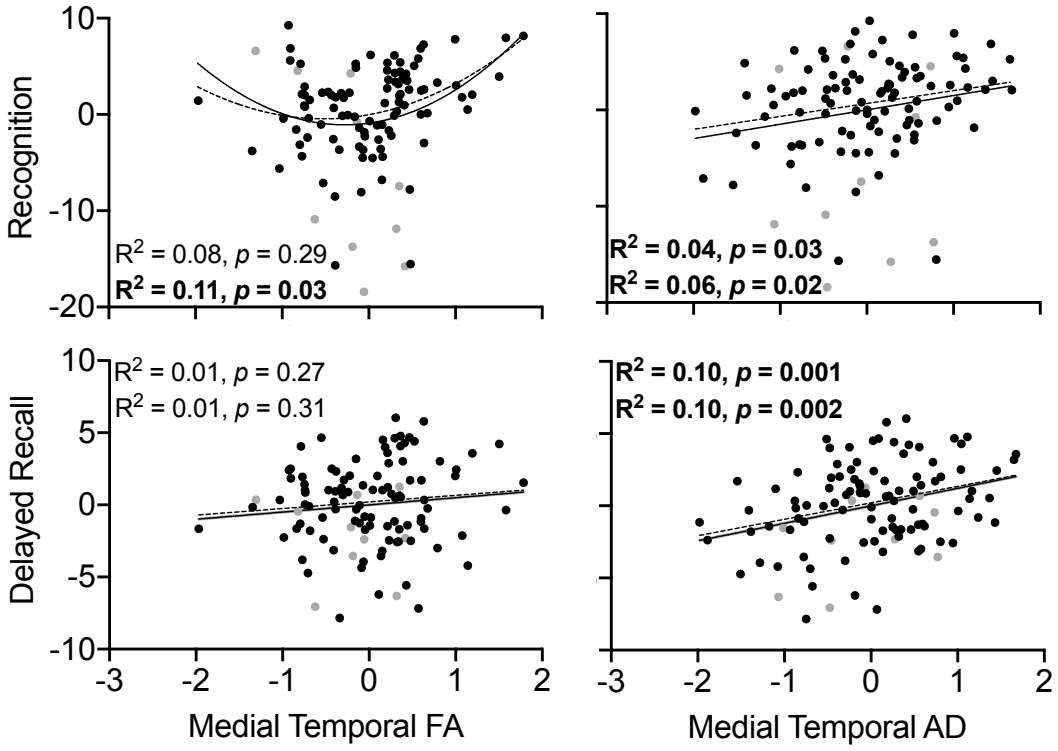

Figure 3. Scatterplots display significant (bolded) relationships between medial temporal fractional anisotropy (FA; left) or axial diffusivity (AD; right) and memory performance (recognition, recall), independent of age, sex, and education, as well as age squared (medial temporal FA versus recognition). 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).

Chapter 2: White Matter Microstructural Correlates of Associative Learning in the Oldest-Old

Abstract

Younger-old adults (ages 65-85 years) exhibit declines in the ability to learn associations between events, which has been attributed to structural degradation of white matter pathways connecting the prefrontal cortex to the hippocampus (e.g., fornix) and striatum (e.g., internal capsule). However, deficits in associative learning abilities may increase in oldest-old adults (ages 90+ years) because advanced age is accompanied by (1) accelerated structural degradation of these white matter pathways and (2) increased prevalence of cognitive impairment. Here, we acquired multicompartment diffusion-weighted magnetic resonance imaging data from 22 oldest-old adults with normal cognition (n = 15; 92.73 ± 1.67 years) or a diagnosis of cognitive impairment no dementia (CIND; n = 7; 93.29 ± 0.76 years) who also completed an associative learning task. Behavioral results revealed significantly better performance during later task stages, as expected if participants incidentally learned the cue-cue-target associations for frequently occurring event triplets. Moreover, better learning performance was significantly predicted by better microstructure of the internal capsule. There was no significant effect of cognitive status on learning performance or white matter microstructure. Thus, associative learning abilities are preserved into the 10th decade of life and can be attributed to individual differences in the microstructure of white matter pathways connecting the prefrontal cortex to the striatum.

Introduction

The ability to form associations between events, even when their relationship cannot be described, is crucial for learning higher-order skills ranging from using new technology to communicating using nonverbal cues (Lieberman, 2000; Seger, 1994). In the laboratory, behavioral evidence of implicit associative learning (IAL) is seen as faster and/or more accurate responses to stimuli that can be predicted based on their relationship to prior events, such as frequently occurring cue-cue-target associations in the Triplet Learning Task (TLT; Howard et al., 2008). IAL has been established in adults across the lifespan, albeit with smaller learning effects in younger-old (65-85 years) relative to young (20-30 years) adults (Bennett et al., 2007; Curran, 1997; Howard et al., 2013, 2008, 2004; Seaman et al., 2013; Simon et al., 2012; Stillman et al., 2016a, 2016c). But IAL has not yet been demonstrated in oldest-old adults (90+ years) in spite of extensive characterization of their impairments across other cognitive domains (Melikyan et al., 2019). Given that IAL is sometimes significant or larger for one dependent measure (reaction time, accuracy) relative to the other in younger age groups (e.g., Bennett et al., 2011; Simon et al., 2012; Stillman et al., 2016a), approaches that take both dependent measures into account, such as rank-ordering binning metrics (Draheim et al., 2016; Hughes et al., 2014), may be more sensitive to subtle learning effects within the oldest-old.

Individual differences in IAL within oldest-old adults may be due to degradation of white matter that connects brain regions involved in learning, which can be measured using diffusion-weighted magnetic resonance imaging (MRI). Previous diffusion work

from our group found that IAL deficits in healthy younger-old adults were associated with age-related declines in the microstructure of white matter tracts connecting the hippocampus and dorsal striatum to the prefrontal cortex (Bennett et al., 2011). These same fronto-hippocampal (e.g., fornix) and fronto-striatal (e.g., internal capsule) white matter tracts exhibit accelerated microstructural declines in advanced age (Merenstein et al., 2021a). Thus, whereas oldest-old adults with lower microstructure in these regions may show minimal evidence of IAL, individuals with higher microstructure should exhibit better IAL performance.

Individual differences in IAL within oldest-old adults may additionally be due to the increased prevalence of cognitive impairment in this advanced age group (Corrada et al., 2008). We previously demonstrated that effects of age on white matter microstructure, as well as relationships between memory performance and microstructure, did not differ significantly between oldest-old adults with normal cognition and those diagnosed with cognitive impairment no dementia (CIND; Bennett et al., 2017; Merenstein et al., 2021a). If similar findings are observed in the current study, it would support the notion that individual differences in IAL in oldest-old adults are attributed to the effects of normal aging, rather than pathological aging. Importantly, assessing these learning effects across participants with normal cognition or CIND increases the generalizability of these findings to the broader oldest-old population, who are often inaccessible for MRI studies of brain aging.

Here, we assessed IAL in nonagenarians for the first time and tested whether IAL performance was related to individual differences in its microstructural substrates and

whether cognitive status affected these associations. Oldest-old adults without dementia, including cognitively normal individuals and those diagnosed with CIND, performed a version of the TLT task. Diffusion-weighted MRI data was also acquired and multicompartment diffusion metrics (i.e., neurite orientation density and dispersion imaging, NODDI; Zhang et al., 2012) were extracted from the fornix and internal capsule. Analyses examined whether oldest-old adults exhibited behavioral evidence of IAL using a rank-ordering binning learning metric that combined their accuracy and reaction time performance (Draheim et al., 2016; Hughes et al., 2014); individual differences in white matter microstructure predicted IAL performance; and cognitive status (cognitively normal versus CIND) affected IAL performance and its relation to white matter microstructure.

Method

Participants

We recruited 28 oldest-old adults (90-98 years, 11 male) that were 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. This included individuals clinically diagnosed as cognitively normal (n = 19) or cognitively impaired no dementia (CIND; n = 9), the latter of which captures individuals with cognitive or functional losses that were not of sufficient severity to meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria for dementia (American Psychiatric Association, 1994; Graham et al., 1997). The clinical evaluation was missing for one 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).

Participants were screened for conditions that would prevent them from being able to enter the MRI scanner (e.g., having ferrous metal implants) and underwent a thorough neurological, physical, and neuropsychological evaluation by trained examiners. We excluded one cognitively normal participant for having a cortical mass that covered large portions of white matter. Using a cutoff of four standard deviations below the mean of the sample, four additional participants (n = 3 cognitively normal, n = 1 CIND) were excluded for responding to too few trials (< 42.7% of all trials) and one participant with CIND was excluded for poor task performance (accuracy < 42.6%). Demographic and neuropsychological data for the final sample of 22 participants (n = 15 cognitively normal, n = 7 CIND) can be found in Table 6, which demonstrates that the subgroups differed in MMSE performance but not age, ethnicity, sex, or years of education completed.

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

Triplet Learning Task

General procedure. Participants completed an abbreviated, deterministic version of an implicit associative learning task (triplet learning task, TLT; Franco et al., 2021; Merenstein et al., 2021b) at their personal residences on a Surface Pro tablet. Completion

of the TLT occurred on average 22.3 ± 15.7 (range 8 – 81 days) days after participants underwent MRI scanning.

Task design. In the TLT, participants viewed four open circles presented in a row on a white background. Each trial, or "triplet", consisted of a cue-cue-target sequence (2850 ms) in which two "cue" circles filled in red (260 ms each) followed by one "target" circle filling in green (1000 ms), with inter-stimulus intervals of 340 ms and inter-trial intervals of 650 ms. Relative to our previous work using this version of the TLT, stimuli were presented at a slower rate for this advanced age group. Participants passively viewed the red cues and were told to respond as quickly and accurately as possible to the location of the green target via the corresponding keyboard response.

Critically, the associations to be learned were between the two cue locations and the green target location of frequently occurring triplets. Twelve unique triplet combinations were randomly selected from the 64 possible cue-cue-target combinations, after excluding 40 triplets that had any two events in the same location (e.g., 111, 112, 121; where the number corresponds to the location of the four circles on the screen from left to right) as their performance reflects pre-existing response tendencies (Boyer et al., 2005; Howard et al., 2008), and after counterbalancing to ensure that cues and targets occurred in each location equally often. Within each block, four triplets were each presented six times (high frequency, HF; 75% of trials) and eight triplets were each presented once (low frequency, LF; 25% of trials). All participants completed a total of 15 32-trial blocks, which were equally divided into five task stages. To prevent fatigue, a self-paced break was provided after each block.

Associative learning measure. Accuracy and reaction times were recorded on each trial for each triplet type (HF, LF). To obtain a measure of IAL, we calculated a rank-ordering binning learning metric that combined the accuracy and reaction time measures (Draheim et al., 2016; Hughes et al., 2014). The first step, which was performed across all task stages but separately within each participant, involved calculating the average reaction time to all accurate LF triplets and subtracting that value from their reaction time to each accurate HF triplet. This yielded difference scores in which lower values indicate that participants responded faster to HF than LF triplets (i.e., better learning). If a participant responded inaccurately to a HF triplet, that specific trial was given a value of 20 as a penalty, regardless of their reaction time (Draheim et al., 2016). Trials that presented a LF triplet or received no response were not given a value. The next step, which was performed across all task stages and all participants, involved compiling the difference and penalty scores for each trial and each participant into one dataset. The combined dataset was then rank ordered into deciles and each score was assigned a bin value ranging from 1 (best performance) to 10 (worst performance). Finally, a single bin score was computed for each task stage by summing all the respective bin values within that task stage, separately for each participant.

Recognition task. A subset of participants (n = 12 cognitively normal, n = 5 CIND) also completed a subsequent computer-based recognition task to test for awareness of the frequently occurring cue-cue-target associations (Franco et al., 2021; Merenstein et al., 2021b). Participants indicated via keyboard responses whether a series of HF, LF, or never presented (no frequency, NF) triplets occurred “frequently”,

"infrequently", or "not at all" during the previously completed version of the TLT. Mean accuracy to each triplet type was calculated separately for each participant.

Imaging Data

Acquisition. Prior to behavioral testing, participants underwent a structural imaging protocol at the University of California, Irvine Facility for Imaging and Brain Research. Imaging data were acquired using a 3T Siemens Prisma MRI scanner fitted with a 32-channel head coil.

A single high-resolution T1-weighted image (magnetization-prepared rapid gradient-echo sequence, MP-RAGE) was acquired with the following parameters: echo time (TE) / repetition time (TR) = 2.72 / 2400 ms, field of view (FOV) = 256 × 256 × 192 mm, matrix size = 320 x 320 x 240, voxel size = 0.8 mm^3, Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) acceleration factor = 2, 208 axial slices, and scan time = 6:28.

A single diffusion-weighted single-shot spin-echo, echo planar imaging image was acquired with the following parameters: TE / TR = 102 / 3500 ms, FOV = 212 × 182 mm^2, matrix size = 128 × 110, voxel size = 1.7 mm^3, multiband factor = 4, 64 slices with no gap, and 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.

Processing. 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, FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) to correct for head movement and eddy-current induced distortions (EDDY), and the

NODDI MATLAB toolbox (https://www.nitrc.org/projects/noddi_toolbox) to obtain diffusion estimates. NODDI provides measures of free diffusion (also known as fraction of isotropic diffusion, FISO), intracellular diffusion (also known as intracellular volume fraction, FICVF, or neurite density index, NDI), and dispersed diffusion (also known as orientation dispersion index, ODI) modeled as an isotropic sphere, sticks, and dispersion of the sticks, respectively (Zhang et al., 2012).

Regions of interest. Based on known anatomical connections from the hippocampus and dorsal striatum to prefrontal cortex (Wakana et al., 2004; Wycoco et al., 2013), we created standard masks of the fornix body and bilateral anterior and posterior limbs of the internal capsule from the JHU ICBM-DTI-81 white matter labels atlas in FSL (Mori et al., 2008). For each participant, these three standard white matter masks were aligned to native diffusion space using the following registration steps: (1) alignment of the MP-RAGE image to the Montreal Neurological Institute (MNI) 152 1mm resolution standard image using an affine transformation with 12 degrees of freedom, (2) alignment of the diffusion image with no diffusion weighting applied (i.e., dtifit_s0) to the MP-RAGE image using a boundary-based registration with six degrees of freedom, (3) concatenation of the diffusion to MP-RAGE and MP-RAGE to MNI transformations, (4) inverting this concatenated transformation, and (5) applying the inverted transformation to align the standard JHU ICBM white matter masks to native diffusion space. The boundary-based registration is based on white matter boundaries that exhibit more reliable age-related changes in signal intensity than gray matter tissue and is therefore fairly robust to pathologies and artifacts seen in diffusion images (Greve and

Fischl, 2009), which is especially important in advanced age. In addition, a trained researcher that was blinded to cognitive status visually inspected the quality of alignments and mask coverage for all three regions of interest, confirming that all masks were of usable quality.

Each region of interest was limited to normal appearing white matter. For each participant, a white matter mask that excludes hyperintense tissue was generated on their MP-RAGE image via FSL's Automated Segmentation Tool (FAST; Zhang et al., 2001), which classifies white matter hyperintensities as either gray matter or cerebrospinal fluid due to their low-intensity values (Melazzini et al., 2021). The partial volume estimate of this white matter mask was thresholded at 0.5, aligned to diffusion space by applying the inversion of the diffusion to MP-RAGE transformation described above, and multiplied by each region of interest mask.

Prior to extracting diffusion metrics, the region of interest masks were further limited to voxels with restricted diffusion below 0.99 to account for artifactual, mathematical errors in regions with insufficient signal (Emmenegger et al., 2021). For each participant, the resulting masks were then separately multiplied by each diffusion metric image (free, intracellular, and dispersed) and values were averaged across voxels within each mask.

Results

Associative Learning Performance

Evidence of IAL was assessed using a repeated measures analysis of variance (ANOVA) with Task Stage (1-5) as a within-person variable and bin scores as the

dependent variable. Results revealed a significant main effect of Task Stage, $F(4, 84) = 9.99$, $p < 0.001$, with significantly higher bin scores for Task Stage 1 (mean = 720.50 ± 204.12) relative to Task Stage 2 (mean = 594.86 ± 112.50; difference = 125.64 ± 153.68), Stage 3 (mean = 589.68 ± 111.26; difference = 130.82 ± 166.02), Stage 4 (mean = 586.82 ± 109.14; difference = 133.68 ± 169.73), and Stage 5 (mean = 599.96 ± 125.76; difference = 120.55 ± 183.81), ps < 0.001 (Figure 4). There were no significant differences observed among the latter four stages, ps > 0.271. Results for the traditional accuracy and reaction time measures are provided in the Supplementary Material (Appendix B), where similar evidence of IAL was seen for accuracy.

Effect of demographic variables. When repeating this ANOVA with sex and years of education as covariates, the main effect of Task Stage remained significant, $F(4, 76) = 11.24$, $p < 0.001$, and there were no significant main effects of or interactions with sex and education, ps > 0.383.

Effect of cognitive status. To test whether cognitive status influenced IAL performance, we repeated the above ANOVA with Cognitive Status (cognitively normal, CIND) as a covariate. The main effect of Task Stage remained significant, $F(4, 80) = 5.43$, $p = 0.001$, and there was no significant main effect of or interaction with Cognitive Status, ps > 0.718.

Awareness of the regularity. To assess whether participants could accurately indicate whether some triplets occurred more often, separate one-sample *t*-tests compared mean recognition accuracy to each Triplet Type (HF, LF, NF) to chance (0.33). Results revealed that accuracy to HF (0.47 ± 0.33), LF (0.27 ± 0.23), and NF (0.40 ± 0.30)

triplets did not differ from chance, *p*s > 0.097. These results provide confidence that participants were not aware of the regularities learned here.

Associative Learning Relates to White Matter Microstructure

Separate linear regressions then tested whether white matter microstructure (free, intracellular, and dispersed diffusion) from each region of interest (fornix body, anterior limb of the internal capsule, posterior limb of the internal capsule) predicted IAL performance. Because IAL performance did not differ among Stages 2 through 5, we used average bin scores across these four task stages as the outcome variable. Significant effects survived Bonferroni correction for comparisons across three diffusion metrics, $p < 0.017$.

Results revealed that worse learning performance (higher bin scores) was significantly associated with higher free, $R^2 = 0.327$, $p = 0.005$, and dispersed, $R^2 = 0.307$, $p = 0.007$, diffusion in the posterior limb of the internal capsule, with a similar trend seen for dispersed diffusion in the fornix body, $R^2 = 0.249$, $p = 0.019$ (Figure 5 and Table 7). No other effects were significant, *p*s > 0.069 (Table 7).

Effect of demographic variables. When repeating these regressions with the addition of sex and years of education as predictors, the above pattern of results did not change, *p*s < 0.018.

Effect of cognitive status. To test whether cognitive status influenced the associations between IAL performance and white matter microstructure, we repeated the above regressions with the addition of Cognitive Status (cognitively normal, CIND) as a predictor. The above pattern of results did not change (Table 7).

Discussion

To our knowledge, this study is the first to examine IAL and its underlying white matter microstructural correlates in nonagenarians. We found that the ability to learn associations between cue-cue-target events is preserved into the 10th decade of life and is supported by better microstructure of the posterior limb of the internal capsule. Results were independent of cognitive status, suggesting that individual differences in IAL and its relation to microstructure were not driven by individuals with early cognitive impairment. Instead, maintaining better microstructure of fronto-striatal pathways may be especially important for IAL abilities in advanced normal aging.

Consistent with behavioral evidence of IAL, oldest-old adults had better learning performance during later (Stages 2 through 5) than earlier (Stage 1) task stages. Finding that learning performance increased across task stages, despite participants being unable to describe the regularity between the cues and targets, is in line with previous studies using the TLT in younger-old adults (Franco et al., 2021; Howard et al., 2008; Merenstein et al., 2021b; Seaman et al., 2013; Stillman et al., 2016b, 2016a). Our observation of preserved IAL in the oldest-old may have been facilitated by specific parameters of the TLT version used here, including the use of a deterministic regularity, fewer unique triplets, longer presentation times, and increased response time window. Thus, future studies using the TLT parameters in younger-old and oldest-old adults will be needed to determine differences in the magnitude of learning across the older adult lifespan. We also used a rank-ordering binning learning metric with the intention of capturing smaller learning effects that may have been distributed across the dependent

measures. Of note, comparable evidence of IAL was seen in the traditional accuracy data (Supplementary Material; Appendix B) and the binning metric was robust to large variability in the traditional reaction time data, possibly resulting from the high prevalence of arthritis in advanced age (Duncan et al., 2011).

In line with our predictions, individual differences in IAL within oldest-old adults were related to difference in microstructure of fronto-striatal and, to some degree, fronto-hippocampal white matter. Specifically, better learning performance (i.e., lower bin scores) was associated with better microstructure (i.e., decreased free and dispersed diffusion) of the posterior limb of the internal capsule. This collection of white matter fibers may be especially important to IAL performance because it relays neural signals between the cortex and basal ganglia regions (putamen, globus pallidum) that have previously been implicated in both earlier and later stages of IAL, including our own functional MRI studies using the TLT (Merenstein et al., 2021b; Simon et al., 2012). Similarly, the trending association between IAL performance and dispersed diffusion in the fornix body may reflect the role of this tract in transmitting neural signals between the prefrontal cortex and hippocampus, which have also been implicated in earlier stages of IAL tasks by functional MRI studies (Dennis and Cabeza, 2011; Merenstein et al., 2021b; Rieckmann et al., 2010; Simon et al., 2012). These results extend prior work using single-tensor diffusion models in younger-old adults (Bennett et al., 2011) by identifying relationships between IAL performance and white matter microstructure in an advanced age group and using multicompartment diffusion modelling. Nonetheless, our interpretations will benefit from future studies assessing these effects within larger

samples of nonagenarians. More broadly, our finding that poorer white matter microstructure predicts poorer IAL performance in a sample of very old adults suggests that age-related white matter degradation interferes with efficient neurotransmission and ultimately contributes to cognitive dysfunction, as predicted by the cortical disconnection hypothesis (Bennett and Madden, 2014; O'Sullivan et al., 2001).

Our results further revealed no significant effect of cognitive status on either the behavioral evidence of IAL or the microstructure-IAL associations. Others have similarly found that IAL in younger-old adults (Boespflug et al., 2014; Moustafa et al., 2012) and that associations between white matter microstructure and age and/or memory performance in larger samples of oldest-old adults (Bennett et al., 2017; Merenstein et al., 2021a) were independent of cognitive status. Together, these findings suggest that individual differences in IAL and its white matter microstructural correlates are unlikely to be attributed to pathologies associated with early cognitive impairment. This interpretation is further supported by our focus on normal appearing white matter at the exclusion of hyperintense tissue, which likely reflects cardiovascular damage and white matter disease (Wardlaw et al., 2015).

In closing, the ability to learn associations between events is spared in oldest-old adults without dementia and can be attributed to individual differences in microstructural properties of fronto-striatal white matter tracts. Because these results were not influenced by diagnoses of CIND, individual differences in IAL and its white matter microstructural correlates likely result from normal aging processes. Given that oldest-old adults represent the fastest growing segment of the population (He and Muenchrath, 2011), the

current investigation lays important groundwork for future MRI studies of brain and neurocognitive aging in this advanced age group.

Table 6. Demographic and neuropsychological test data.

Mean (SD)	Whole Sample	CIND	Normal	t / χ^2
N	22	7	15	n/a
Age	92.91 (1.44)	93.29 (0.76)	92.73 (1.67)	0.83
N Female (%)	14 (64%)	4 (57%)	10 (67%)	0.19
N Hispanic (%)	2 (9%)	1 (14%)	1 (7%)	0.34
Education (years)	15.55 (2.89)	16.00 (3.0)	15.33 (3.2)	0.50
MMSE	26.18 (2.86)	24.0 (3.1)	27.2 (2.0)	**2.83**

Notes. Data are presented as mean (standard deviation, SD), separately for participants with cognitive impairment no dementia (CIND) or normal cognition. Significant group differences at $p < 0.05$ are indicated by bolded t or χ^2 (N female, N Hispanic) statistics. MMSE = Mini Mental State Examination.

Table 7. Associations between IAL and white matter microstructure.

	Whole sample (R^2)			Controlling for CIND (R^2)		
Region	Restricted	Hindered	Free	Restricted	Hindered	Free
Fornix body	0.082 (0.197)	*0.246 (0.019)*	0.156 (0.069)	0.112 (0.147)	*0.249 (0.023)*	0.166 (0.071)
Anterior limb of internal capsule	0.014 (0.606)	0.006 (0.722)	0.115 (0.122)	0.023 (0.559)	0.009 (0.776)	0.117 (0.137)
Posterior limb of internal capsule	0.010 (0.656)	**0.307 (0.007)**	**0.327 (0.005)**	0.015 (0.656)	**0.255 (0.005)**	**0.343 (0.006)**

Notes. Significant (bolded, Bonferroni corrected $p < 0.017$) and trending (italics, $p < 0.05$) relationships [R^2 (p)] between learning performance and white matter microstructure are presented separately for each diffusion metric (restricted, hindered, free) and region of interest.

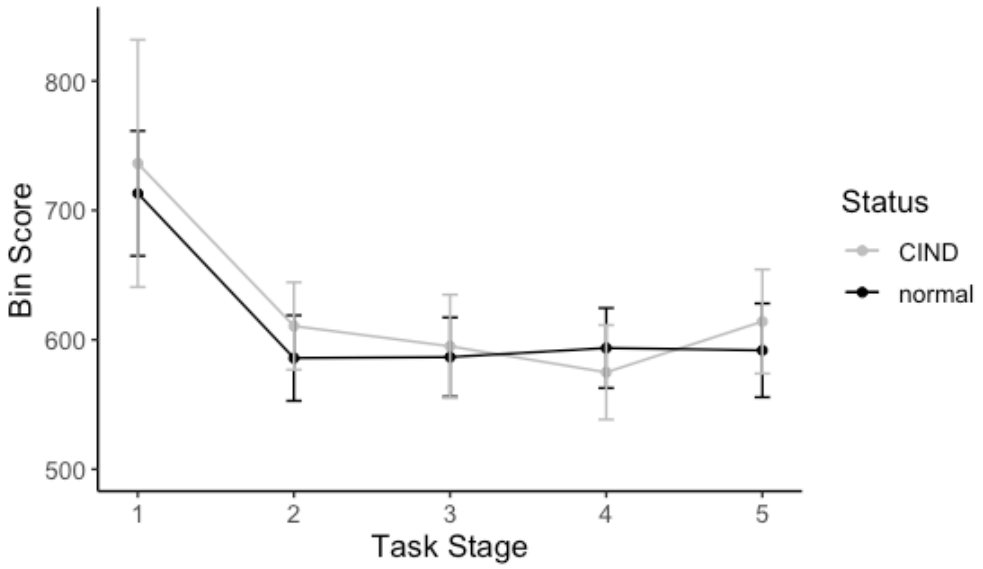

Figure 4. Behavioral results are displayed as a function of Task Stage, separately for oldest-old adults with normal cognition (normal; black) or cognitive impairment no dementia (CIND; gray). Significant evidence of IAL was seen as significantly lower bin scores for Stages 2 through 5 when compared to Stage 1. Error bars represent standard error of the mean.

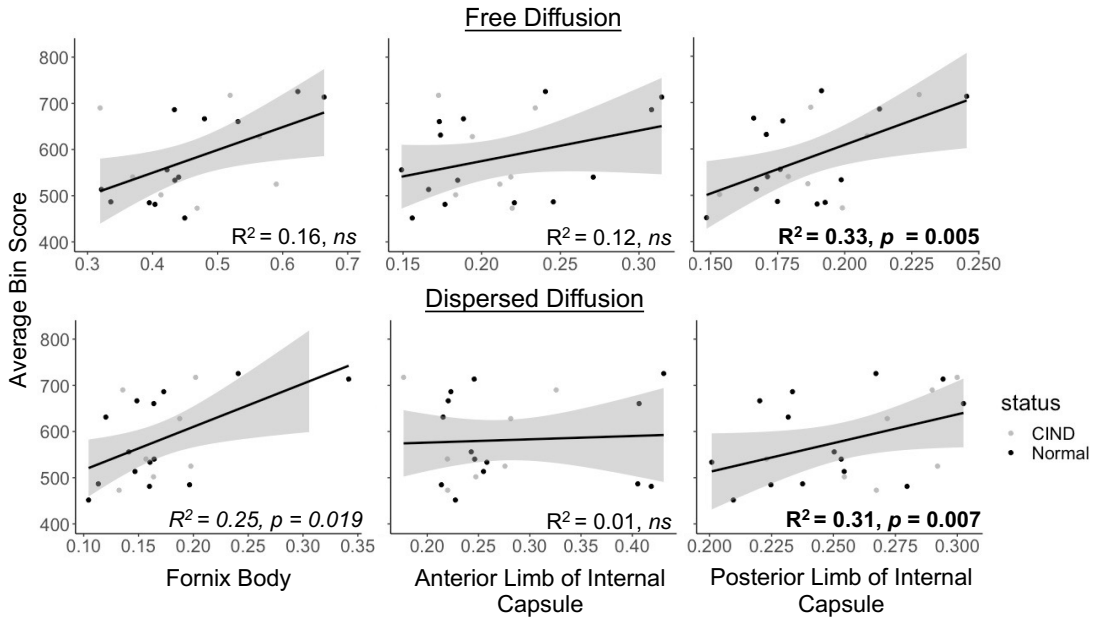

Figure 5. Scatterplots show the significant (bolded, $p < 0.017$) and trending (italics, $p < 0.05$) regression lines and coefficients of determination (R^2) from the analyses between free (top) or dispersed (bottom) diffusion and average bin scores, separately for each region of interest. Results revealed that better microstructure (i.e., decreased free and dispersed diffusion) of the posterior limb of the internal capsule predicted significantly better learning (i.e., lower bin scores). A similar trend was seen for dispersed diffusion in the fornix body. Oldest-old adults with normal cognition or cognitive impairment no dementia (CIND) are displayed as black or gray circles, respectively. The shaded gray area represents 95% confidence intervals.

Chapter 3: Bridging Patterns of Neurocognitive Aging Across the Older Adult Lifespan

Abstract

Magnetic resonance imaging (MRI) studies of brain and neurocognitive aging rarely include oldest-old adults (ages 80+). But predictions of neurocognitive aging theories derived from MRI findings in younger-old adults (ages ~55-80) may not generalize into advanced age, particularly given the increased prevalence of cognitive impairment/dementia in the oldest-old. Here, we reviewed the MRI literature in oldest-old adults and interpreted findings within the context of regional variation, compensation, brain maintenance, and reserve theories. Structural MRI studies revealed regional variation in brain aging as larger age effects on medial temporal and posterior regions for oldest-old than younger-old adults. They also revealed that brain maintenance explained preserved cognitive functioning into the tenth decade of life. Very few functional MRI studies examined compensatory activity in oldest-old adults who perform as well as younger groups, although there was evidence that higher brain reserve in oldest-old adults may mediate effects of brain aging on cognition. Despite some continuity, different cognitive and neural profiles across the older adult lifespan should be addressed in modern neurocognitive aging theories.

1. Introduction

Oldest-old adults beyond 80 years of age represent the fastest growing segment of the population in most developed countries (He and Muenchrath, 2011). However, previous neuroimaging studies have primarily related measures of brain aging to cognitive performance in younger-old adults aged ~55-80 years. Numerous impactful theories of neurocognitive aging have been derived from these earlier studies, but their predictions based on younger-old cohorts may not generalize to oldest-old cohorts. The few studies extending into advanced age primarily focus on disease-related brain and neurocognitive changes seen in oldest-old adults with cognitive impairment (Corrada et al., 2010, 2008; Yang et al., 2013). Even less is known about cognitively normal oldest-old adults, ~50% of whom have no evidence of brain pathologies (Kawas et al., 2015). Furthermore, the large heterogeneity of normal brain aging across the older adult lifespan (Eavani et al., 2018; Poulakis et al., 2021) may differentially affect cognitive and neural measures in oldest-old compared to younger-old adults. It is therefore important to consider the degree to which extant neurocognitive aging theories account for findings reported in advanced age.

Magnetic resonance imaging (MRI) is a neuroimaging technique that is well suited for examining age-related differences in brain structure and function in advanced age and determining whether such neural differences are predictive of cognitive deficits (Hartel and Buckner, 2006; Young et al., 2020). Advantages of MRI include it being readily available, cost-effective, and non-invasive relative to other neuroimaging techniques, such as positron emission tomography (PET), computerized tomography

(CT), near infrared spectroscopy (NIRS), and electro- and magneto-encephalography (EEG/MEG). Individual MRI scans are relatively short (3-8 minutes), with structural scans requiring nothing more than having participants lie still for the duration of the scan session (15-45 minutes). Padding and other accommodations (e.g., blankets, nonferrous glasses, ear buds) can make the experience more comfortable (e.g., for those with spine curvature), not just more accessible, for individuals with various physical issues (e.g., vision problems, arthritis).

Multiple MRI modalities can also be acquired from participants during a single scanning session, which allows studies to obtain varied measures of brain structure and function. For example, one common MRI modality is high-resolution T1-weighted images, which can reveal age-related differences in the degree of atrophy (volume, morphometry) of gray and white matter (Anderson et al., 2005). Diffusion tensor imaging (DTI) provides more detailed estimations of microstructural tissue properties by measuring the jitter (diffusion) of molecular water (Beaulieu, 2002; Jones, 2008; Mori and Zhang, 2006). Damage to white matter tissue can be further probed by estimating the volume of white matter hyperintensities (WMH) using fluid attenuated inversion recovery (FLAIR) sequences (Lockhart and DeCarli, 2014). On the other hand, age-related differences in brain activity can be inferred using functional MRI (fMRI), which provides estimates of the blood-oxygen-level-dependent (BOLD) signal that can either be acquired during performance of a cognitive task (i.e., task-based fMRI; Logothetis, 2008) or during rest (i.e., resting state fMRI; Cole et al., 2010). In addition to the advantages noted above, this array of modalities makes MRI an ideal tool to examine the neural

mechanisms affected by advanced age and whether their contributions to cognition differ across the older adult lifespan.

Other reviews on the oldest-old have focused on broader neuroimaging findings (i.e., including both CT and PET studies; Woodworth et al., 2021), problems related to frailty and cardiovascular disease (Rosa et al., 2020), risk factors of dementia (Gardner et al., 2013; Paolacci et al., 2017; Pierce and Kawas, 2017), methodological considerations (Poon et al., 2007), and the epidemiology and pathology of dementia (Gardner et al., 2013; Kawas et al., 2021; Von Gunten et al., 2010; Yang et al., 2013). The current review will add to this literature by (1) reviewing neuroimaging studies of brain and neurocognitive aging in the oldest-old, (2) evaluating whether these findings align with select neurocognitive aging theories and findings in younger-old adults, and (3) providing methodological considerations and ideas for future neuroimaging research in the oldest-old. Ultimately, this review will demonstrate that the extant literature is sufficient large to identify areas of convergence and call for areas that will benefit from further study, with particular attention to the methodological concerns discussed here.

2. Scope of Review

We conducted our review between May and July 2021 with PubMed searches using both an age ("oldest old", "old old", "very old", "centenarians", "nonagenarians", "octogenarians", "ag*ing", "80 and over") and MRI ("magnetic resonance imaging", "MRI", "brain") term, with these searches repeated after adding a cognition term ("dementia", "cognition", "cognitive performance"). We selected studies that met the following criteria: (1) English language publications up to 2021, (2) involved human

subjects, (3) original research reports, (4) included adults over 80 years old, and (5) examined effects of age on an MRI measure of brain structure or function and/or relationships between chronological age and cognitive performance. Studies were further limited to those assessing these effects within older age groups (e.g., ages 55+ years old), with lifespan studies (e.g., ages 20-80+ years) only included when their results were disaggregated by an oldest-old adult subgroup (e.g., conducting analyses with and without oldest-old adults or examining effects separately within oldest-old adults).

2.1 Defining the "oldest-old"

The definition of oldest-old adults varies across research groups, with the Sydney Memory and Aging Study (Piguet et al., 2003; Z. Yang et al., 2016b) and Health, Aging, and Body Composition Study (Rosano et al., 2005a, 2005b; Simonsick et al., 2001) including individuals greater than 80 years old, whereas The 90+ Study (Kawas and Corrada, 2006) is limited to individuals greater than 90 years of age. Because normal aging (e.g., neurodegeneration, small vessel disease) and dementia-related (e.g., amyloid-beta plaques, neurofibrillary tangles; Braak and Braak, 1997) pathology are both less prevalent in octogenarians (80-89 years) than nonagenarians (90-99 years)(Kawas et al., 2015; Yang et al., 2013), one could argue that the latter group represents a more stringent definition of the oldest-old. Nonetheless, to better integrate findings across these cohorts, the current review defined oldest-old adults as individuals beyond 80 years of age.

Studying the oldest-old provides an opportunity to assess how their increased prevalence of cognitive impairment no dementia (CIND) affects MRI measures of brain aging (Brookmeyer et al., 2017; Corrada et al., 2010, 2008). Relative to oldest-old adults

with normal cognition, those with CIND are at increased risk of progressing to dementia (Peltz et al., 2011), which we assume reflects a relatively greater accumulation of dementia-related pathology contributing to their clinical expression of cognitive deficits. To disentangle these distinct but related constructs, however, we suggest that future MRI studies examining cognitive status subgroup differences in this age group simultaneously assess Alzheimer's disease risk factors (e.g., e4 allele combination on the apolipoprotein [APOE] gene) and pathology (e.g., amyloid-beta).

2.2 Overview of neurocognitive aging theories

The body of this review is divided into four sections covering studies that assessed gray matter volumetry and morphometry (Section 3), white matter hyperintensities and microstructure (Section 4), fMRI activity (Section 5), or other MRI modalities (Section 6) in the oldest-old. Each section separately reviews the literature examining brain aging (Table 1), neurocognitive aging (Table 2), and cognitive status subgroups (Table 3) in the oldest-old using the corresponding MRI modality. Findings within each subsection are then discussed in relation to the following four theories, the latter of which is only discussed in the fMRI section (Table 4): regional variation of brain aging (Raz et al., 2010; West, 1996), brain maintenance (Nyberg et al., 2012), brain reserve (Barulli and Stern, 2013), and compensation (Cabeza, 2002; Cabeza et al., 2018; Grady, 2008; Reuter-Lorenz and Cappell, 2008). These neurocognitive aging theories were selected for their ability to make specific predictions that could be applied to MRI data in the oldest-old. Each theory is briefly introduced below.

2.2.1 Regional variation of brain aging

Numerous theories in younger-old adults propose that the magnitude of age effects varies across the brain, particularly in frontal and medial temporal regions. One influential theory, the frontal lobe hypothesis, proposed that healthy aging disproportionately affects anterior brain regions, resulting in worse performance on cognitive processes supported by the prefrontal cortex (e.g., executive functioning; West, 1996). An extension of this view proposes an anterior-to-posterior gradient in normal brain aging such that age effects in younger-old adults are largest and appear earliest in frontal regions, with parietal and occipital regions being relatively preserved until advanced age (Cabeza and Dennis, 2014; Davis et al., 2009; Head et al., 2004; Hedden and Gabrieli, 2004; Madden et al., 2009; Pfefferbaum et al., 2005). However, others report similarly large age-related differences in medial temporal regions such as the hippocampus and entorhinal cortex in younger-old adults, which have been associated with episodic memory deficits (for reviews, see Craik and Rose, 2012; Jagust, 2013; Tromp et al., 2015).

An important question, particularly when applying these theories to the oldest-old, is whether frontal lobe atrophy occurs in both normal aging and dementia, whereas medial temporal lobe atrophy primarily occurs in individuals with dementia (Head et al., 2005; Hedden and Gabrieli, 2005; Resnick et al., 2003). This distinction arose from the latter regions being among the first to accumulate dementia-related pathologies (e.g., amyloid-beta plaques, neurofibrillary tangles; Braak and Braak, 1997). Yet other work suggests that frontal and medial temporal regions are similarly affected by normal aging (Fjell et al., 2014; Raz et al., 2010, 2005), as both regions have smaller diameter axons

and lower oligodendrocyte-to-axon ratios making them more vulnerable to degeneration (Stebbins and Murphy, 2009), as well as a delayed time course for myelination (Bartzokis, 2004). The MRI literature in oldest-old adults may contribute to this debate by comparing medial temporal regions in individuals at low versus high risk for dementia, the latter of which includes those diagnosed with CIND.

Regional variation in brain aging within oldest-old adults may present as frontal and medial temporal vulnerability similar to younger-old adults, consistent with the notion that these regions decline across the older adult lifespan. Relative to younger-old adults, larger age effects in medial temporal regions may reflect an accumulation of dementia-related pathology in both cognitively normal and CIND oldest-old adults. However, an open question is whether additional regions that are relatively preserved in younger-old adults, such as parietal and primary sensory areas, are vulnerable in advanced age.

2.2.2 Brain maintenance

Brain maintenance is a theory proposing that younger-old adults with cognitive abilities similar to younger adults (e.g., 20-30 years) or better than age-expected norms experience minimal age-related brain changes and a relative lack of brain pathology (Nyberg et al., 2012; Nyberg and Pudas, 2018). In other words, these cognitively normal older adults have "maintained" a young-like brain, which is comparable to the term "resistance" often used in Alzheimer's disease biomarker research (Montine et al., 2019). For example, one study found similar prefrontal recruitment when comparing younger-old adults who performed well on a memory task to younger and middle-aged (e.g., 30-

55 years) adults (Vidal-Piñeiro et al., 2018). These same top-performing younger-old adults also had no significant decline in memory performance and slower rates of entorhinal cortical atrophy measured over eight years, suggesting that these substrates helped preserve memory function. However, very few studies have interpreted similar effects in light of brain maintenance in advanced age.

Brain maintenance may generalize to oldest-old adults. Support for this view would include structural MRI studies finding that oldest-old adults with the best cognitive performance also have the largest brain volumes, intact tissue microstructure, and fewer WMH, especially longitudinally. It might also include fMRI studies finding that top-performing oldest-old adults with little structural degradation recruit similar brain networks to a comparable degree as younger age groups, as noted above.

2.2.3 Brain reserve

Brain reserve has been proposed as a mechanism to account for individual differences in cognitive aging in younger-old adults and is similar to the term "resilience" used in Alzheimer's disease biomarker research (Montine et al., 2019). The idea is that cognitive impairment will not be observable until changes in the brain, like those associated with aging and dementia, exceed some threshold that varies across individuals depending on their "brain reserve", such as their brain size, neurite density, or synaptic connections (Barulli and Stern, 2013). Thus, older individuals with high brain reserve may be cognitively normal despite having a large amount of age-related degradation or accumulation of pathology. This differs from brain maintenance, which proposes that

individuals with normal cognition should have an absence of age-related brain changes or disease-related pathologies.

In the oldest-old, brain reserve theories may explain structural MRI studies finding that a given level of neural degradation (e.g., atrophy, WMH burden) results in cognitive impairment for individuals with low brain reserve, whereas those with high brain reserve will continue to present as cognitively normal (Barulli and Stern, 2013; Tucker and Stern, 2011). It may also be used to interpret fMRI studies finding that oldest-old adults with similar cognitive performance relative to younger age groups have similar or even reduced BOLD activity in the face of marked structural degradation. This pattern has previously been interpreted as a form of functional reserve against age-related brain changes, potentially reflecting more efficient use of the spared brain tissue in pre-existing networks (Barulli and Stern, 2013; Stern, 2006).

2.2.4 Compensation

As defined in a recent consensus paper (Cabeza et al., 2018), compensation theories propose that younger-old adults may compensate for the negative effects of brain aging by increasing activity in the same and/or additional brain regions relative to younger adults, allowing them to perform well on the cognitive tasks (Cabeza et al., 2018; Davis et al., 2008; Grady, 2008). One of the earliest compensation theories is Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002), which described the finding that high performing older adults recruited bilateral prefrontal regions relative to younger adults and low performing older adults who recruited unilateral regions during memory performance (Cabeza et al., 1997). Compensation-

Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz and Cappell, 2008) further proposes that older adults show compensatory activity when task demands are low and they can perform well, but fail to show compensatory activity when task demands are high and they perform worse than younger adults. This is thought to result from older adults reaching a ceiling of neural resources that can be recruited when tasks are more difficult. As with regional variation theories, compensatory activity is often seen in frontal brain regions.

Compensatory neural activity in the oldest-old should look similar to patterns seen in younger-old adults, with more BOLD activity in individuals whose cognitive performance is comparable to younger age groups. However, it is possible that compensatory activity may not be seen in oldest-old adults if their performance is always worse than younger age groups. Such a finding would be consistent with CRUNCH if it reflects task demands being higher in advanced age.

3. Gray matter volumetry and morphometry

3.1 Brain aging in the oldest-old

Because the literature on white matter volume in the oldest-old consists of too few studies to draw consistent conclusions (Salat et al., 1999; Stickel et al., 2018; Z. Yang et al., 2016a), this section instead focused on studies assessing the effect of advanced age on gray matter volume and morphometry (cortical thickness, sulcal width). These studies have revealed three key findings: (1) negative effects of age on volume were consistently seen for the hippocampus, (2) less consistent and possibly weaker age effects on volume and mophometry were seen in other medial temporal and frontal regions, and (3) the

negative effects of age were comparable in oldest-old adults with normal and superior cognitive status. The literature supporting these findings is described below and summarized in Table 8.

Most studies reported that advanced age was accompanied by smaller volume of the hippocampus (Mueller et al., 1998; van Bergen et al., 2018; Z. Yang et al., 2016a), a medial temporal structure commonly linked to memory ability, with this negative effect of age on hippocampal volume being significantly greater than in the prefrontal cortex (Yang et al., 2016a). Together, this suggests that there are consistent and large effects of advanced age on hippocampal volume relative to younger-old adults, similar to lifespan studies extending into advanced age (Jernigan et al., 2001; Langnes et al., 2020).

As in the hippocampus, advanced age-related degradation has been observed in other medial temporal and brain-wide structures. Relative to younger-old adults, oldest-old adults have significantly smaller volumes (Brickman et al., 2008) and greater thinning (Z. Yang et al., 2016a) of the entorhinal cortex, as well as smaller temporal lobe volumes (Mueller et al., 1998). There are also longitudinal decreases in temporal (and frontal) cortical thickness when following oldest-old adults over a four-year period (Li et al., 2020). Although at least one study found no significant effect of age on entorhinal volume within older adults (van Bergen et al., 2018). Beyond medial temporal structures, the sulcal width of both anterior (e.g., anterior cingulate, superior frontal) and posterior (e.g., intraparietal, posterior cingulate) regions was greater for oldest-old than younger-old adults (Tang et al., 2021). Indeed, effects of advanced normal aging on anterior neural tissue appears to be distinct from disease, as one study observed significantly greater

volume loss in the prefrontal cortex for cognitively normal oldest-old adults than younger-old adults with normal cognition or those with Alzheimer's disease (Salat et al., 1999). Together, these findings suggest brain-wide effects of advanced age on gray matter volume and morphometry.

When examining these age effects across cognitive status subgroups, one study observed that even older adults with superior cognitive status experienced whole brain volume loss and cortical thinning, with the largest age effects in the hippocampus and entorhinal cortex (Z. Yang et al., 2016a). This finding suggests that some degree of advanced age-related degeneration in the hippocampus, among other brain regions, may be characteristic of normal aging. However, additional research with oldest-old adults across cognitive status subgroups is needed to better understand the extent to which volume and morphometry differences reflect normal aging or preclinical dementia, especially those that can also assess Alzheimer's disease risk factors and pathology (e.g., APOE genotype, amyloid-beta).

In summary, the current findings suggest a more brain-wide vulnerability in advanced age that is especially marked in the hippocampus. This pattern of results is not inconsistent with neurocognitive aging theories in younger-old adults, such as the anterior-to-posterior gradient (Davis et al., 2009; Head et al., 2004; Hedden and Gabrieli, 2004; Madden et al., 2009), in that advanced age effects on volume and morphometry also extended to anterior and posterior cortical regions (Li et al., 2020; Tang et al., 2021; Z. Yang et al., 2016a). Yet this view does not account for the predominant pattern of hippocampal degradation seen in advanced aging (Z. Yang et al., 2016a). Instead, the

findings reviewed here suggest that an anterior-to-posterior gradient may be more common in early aging. Future studies examining age effects using the same structural imaging modality across the older adult lifespan are needed to better understand the time course of degradation in anterior (frontal cortex), medial temporal (hippocampus), and posterior (parietal cortex) regions. In turn, extant theories of regional variation in brain aging may need to account for the increased hippocampal-specific and brain-wide susceptibility to advanced age.

3.2 Neurocognitive aging in the oldest-old

Studies examining the effect of brain volume and morphometry on cognition in advanced age have primarily focused on episodic memory and processing speed performance. Their results have predominantly revealed positive associations with hippocampal volume or medial temporal cortical thickness using a variety of study designs (cross-sectional, longitudinal) and age groups (entire lifespan, older adult lifespan, oldest-old only). The literature supporting these findings is described below and summarized in Table 9.

Slower rates of episodic memory decline assessed longitudinally have been reported within oldest-old adults with fewer changes in hippocampal volume (Legdeur et al., 2019) and higher baseline medial temporal and anterior cingulate cortical thickness (Pelkmans et al., 2021). Slower rates of memory decline have also been associated with larger baseline whole brain volume across the older adult lifespan (Carmichael et al., 2012). Cross-sectional studies similarly report that oldest-old adults with larger hippocampus volumes have better episodic memory performance (Eguchi et al., 2019)

and faster processing speeds (Legdeur et al., 2020; Pelkmans et al., 2021), comparable to what has been reported in younger-old adults (Carr et al., 2017; Gorbach et al., 2017; O'Shea et al., 2016). Larger volume of the hippocampus was also found to predict better memory performance in individuals across the lifespan (ages 4-93 years; Langnes et al., 2020). However, the effects in anterior hippocampus were driven by individuals aged 80+ years, suggesting that this subregion of the hippocampus may be especially important for memory function in advanced age.

In summary, larger gray matter volumes and morphometry, primarily of the hippocampus and medial temporal lobe, relate to better performance on episodic memory and processing speed tasks across the lifespan and into advanced age. Because these studies revealed better cognitive performance in oldest-old adults with either minimal age-related brain changes assessed longitudinally or minimal structural degradation assessed cross-sectionally (e.g., larger volume, thicker cortex), their findings are consistent with the brain maintenance theory (Nyberg et al., 2012). Specifically, as in younger-old adults, maintenance of a young-like brain in advanced age may prevent cognitive aging. Future work extending beyond medial temporal regions and episodic memory processes can help test the functional role of frontal and posterior brain aging (e.g., using executive function or attention-based paradigms) in oldest-old relative to younger-old adults, especially those using longitudinal designs.

3.3 Cognitive status subgroups in the oldest-old

Several studies have compared volumetry and morphometry measures between subgroups of oldest-old adults that differ in cognitive status, defined as normal cognition,

cognitive impairment, or dementia. These studies have revealed similar effects of cognitive status across the older adult lifespan in medial temporal regions (hippocampus, entorhinal cortex, parahippocampal gyrus), although the effect of cognitive status on volume and morphometry in cortex (temporal, parietal) may be smaller in oldest-old than younger-old adults. The literature supporting these findings is described below and summarized in Table 10.

Larger hippocampal volumes are consistently seen for oldest-old adults with normal cognition relative to those with cognitive impairment or dementia (Barkhof et al., 2007; Gosche et al., 2002; Holland et al., 2012; Lopez et al., 2014; Z. Yang et al., 2016b), similar to findings in younger-old adults (Apostolova et al., 2012; Z. Yang et al., 2016b). Larger volumes of the hippocampus, as well as entorhinal cortex and parahippocampus gyrus, have also been seen for oldest-old adults with preserved general cognitive performance over 10 years than those who declined, with comparable effects in younger-old adults (Rosano et al., 2012). However, at least one study found that brain regions showing a volumetric effect for normal versus impaired cognitive status differed in oldest-old (hippocampus, inferior frontal gyrus, temporal pole) relative to younger-old (putamen, parahippocampal gyrus, cortex) adults (Z. Yang et al., 2016b). Smaller differences between cognitively normal and dementia subgroups have also been reported for thickness (Stricker et al., 2011) and volume (Holland et al., 2012) of temporal-parietal regions for oldest-old relative to younger-old adults. A more complete picture of the structural signatures of normal aging versus dementia will require future studies that

compare cognitive status subgroups in younger-old and oldest-old populations using the same MRI metrics.

In summary, these findings are generally in line with brain reserve, which would expect cognitively normal individuals to have higher brain reserve (e.g., larger brain volumes) than those with cognitive impairment or dementia. Whereas some degree of atrophy may be characteristic of normal aging (Z. Yang et al., 2016a), more accelerated degradation as a function of cognitive status, particularly in the medial temporal lobe, is consistent with its role in dementia across the older adult lifespan. However, these findings further suggest that levels of reserve are not uniform across the brain and that regional differences may be exacerbated in advanced age, which warrants further investigation.

4. White matter hyperintensities and microstructure

4.1 Brain aging in the oldest-old

Effects of advanced age on WMH and microstructure have been assessed across the older adult lifespan and within the oldest-old only, using a variety of cognitive status subgroups (superior, normal, impaired). These studies have revealed three key findings: (1) WMH accumulate more in oldest-old relative to younger-old adults predominantly in posterior brain regions, (2) worse tissue microstructure (i.e., lower fractional anisotropy, FA; higher diffusivity) is seen in oldest-old relative to younger-old adults that is most prominent in medial temporal regions, and (3) these effects of age on WMH and microstructure do not vary between oldest-old adults with normal or impaired cognitive

status. The literature supporting these findings is described below and summarized in Table 8.

One study examining WMH across the older adult lifespan found quadratic age-related differences for all four cortical lobes (Z. Yang et al., 2016a), indicating an accelerated accumulation of WMH in advanced age. Specific vulnerability of the frontal lobe was supported by one study limited to this region finding significantly higher WMH burden for oldest-old adults > 91 years than those < 90 years old (Polvikoski et al., 2010). However, when examining WMH across the brain within oldest-old adults, there was significantly higher WMH burden in the parietal than the frontal lobe (Piguet et al., 2003). Thus, whereas there are larger brain-wide WMH differences in advanced age relative to younger adults, parietal regions may be most sensitive to age-related WMH accumulation in the ninth and tenth decades.

Studies examining white matter microstructure have reported negative age effects on frontal, temporal, and parietal regions across the older adult lifespan (Lövdén et al., 2013), as well as within oldest-old adults over a two-year period (Lövdén et al., 2014). Our own work in younger-old and oldest-old adults revealed quadratic age-related differences in white matter microstructure across the brain that were more pronounced in advanced age, with the largest effects seen for the medial temporal lobe (Merenstein et al., 2021a). These findings extended earlier work in which we found the largest age effects for medial temporal (fornix) and posterior (splenium) white matter tracts within oldest-old adults (Bennett et al., 2017). As such, there are consistently large effects of

advanced age on medial temporal white matter relative to younger-old adults and even amongst only oldest-old adults.

There is some evidence that advanced age-related WMH accumulation and microstructural degeneration is not driven by oldest-old with cognitive impairment or dementia. For example, the previously mentioned age-related increases in brain-wide WMH were observed even in older adults with superior cognition (Z. Yang et al., 2016a), and the larger age effect on parietal than frontal WMH was independent of APOE genotype (Piguet et al., 2003). Moreover, our findings of brain-wide age effects on microstructure across the older adult lifespan (Merenstein et al., 2021a) and within only oldest-old adults (Bennett et al., 2017) did not change after excluding oldest-old adults diagnosed with CIND. Thus, brain-wide microstructural degradation seen in advanced age cannot solely be attributed to cognitive dysfunction or increased dementia risk in this age group.

In summary, finding greater age effects on posterior regions differs from the predominantly frontal findings in younger-old adults, but together they support an anterior-to-posterior gradient to white matter aging (Head et al., 2004; Hedden and Gabrieli, 2004; Madden et al., 2009). Importantly, there was nonlinear white matter degradation in medial temporal and posterior regions within oldest-old adults regardless of CIND or superior cognitive status, which might reflect an acceleration of normal aging processes in advanced age (e.g., demyelination, myelin ballooning, cardiovascular damage; Peters, 2002; Wardlaw et al., 2015). These findings are consistent with the gray matter volumetry and morphometry studies reviewed in Section 3.1, thereby providing

converging evidence for a brain-wide vulnerability in advanced age that spans multiple neural substrates captured by these different MRI modalities. Because most studies examining WMH and microstructure in the oldest-old have used cross-sectional designs (c.f., Lövdén et al., 2014), this line of work could be progressed by future longitudinal studies that can track these brain aging effects over time into advanced age.

4.2 Neurocognitive aging in the oldest-old

Numerous cross-sectional and longitudinal studies have shown that fewer WMH and better microstructure (e.g., higher FA, lower diffusivity) relates to better cognitive performance into advanced age, with the most studied cognitive domains being episodic memory, executive functions, and processing speed. The literature supporting these findings is described below and summarized in Table 9.

For episodic memory, oldest-old adults with slower rates of memory decline had fewer baseline WMH across the brain (Pelkmans et al., 2021), with this association being particularly strong within the frontal lobe (Piguet et al., 2003). Better episodic memory performance has also been related specifically to better medial temporal white matter microstructure (Merenstein et al., 2021a), as well as better hippocampal gray matter microstructure (Reas et al., 2021), across the older adult lifespan. For executive functions, older adults who accumulated fewer brain-wide WMH over time had smaller declines in performance (Carmichael et al., 2012), although the association between WMH burden and executive functions may be weaker in oldest-old adults (Legdeur et al., 2019). For processing speed, faster performance within oldest-old adults has been associated with fewer brain-wide WMH (Pelkmans et al., 2021) and better microstructure

of the corticospinal tract (Lövdén et al., 2014), uncinate and superior longitudinal fasciculi (Rosano et al., 2015), and whole brain white matter (Venkatraman et al., 2011). Associations between microstructure and processing speed in individuals across the older adult lifespan remained significant after accounting for the future development of dementia (Haynes et al., 2017) or excluding individuals meeting criteria for preclinical dementia (Laukka et al., 2013), suggesting that these effects are not solely driven by early cognitive impairment.

Altogether, these patterns would be predicted by brain maintenance theory, where preserved cognitive functioning should be observed among older adults with minimal changes in markers of brain aging. One interesting finding that requires further investigation is reports of race (Liu et al., 2015) and sex (Reas et al., 2021) differences in relationships between performance and WMH or microstructure. Findings such as smaller WMH volumes relating to faster processing speeds for Black but not White younger-old and oldest-old adults (Liu et al., 2015) may be due to the larger WMH volumes seen among Black (and Hispanic) relative to White individuals across the older lifespan (Brickman et al., 2008). Future studies using more diverse oldest-old samples are needed to determine whether race and sex moderate the association between the previously reported MRI markers and cognition in advanced age.

4.3 Cognitive status subgroups in the oldest-old

Studies comparing WMH and microstructure measures between subgroups of oldest-old adults that differ in cognitive status (normal cognition, cognitive impairment, dementia) report a weakened ability of these measures to differentiate these subgroups in

the oldest-old. The literature supporting this finding is described below and summarized in Table 10.

A handful of studies have shown that whole brain WMH volumes do not significantly differ between cognitively normal and impaired subgroups within oldest-old adults (Tanskanen et al., 2013; Zamboni et al., 2019) or across younger-old and oldest-old adults (Z. Yang et al., 2016b). Longitudinally, baseline whole brain WMH burden in individuals across the older adult lifespan was comparable for those who had preserved and declining general cognitive performance over a 10-year period (Rosano et al., 2012). Comparable effects have been reported for whole brain white matter microstructure, which differed between cognitively normal and impaired subgroups of younger-old, but not oldest-old, adults (Zamboni et al., 2019). However, region-specific differences between oldest-old adults with normal and impaired cognition may have been obscured by the use of whole brain WMH measures as one study limited to the frontal lobe observed fewer WMH for oldest-old adults with normal cognition than those diagnosed with Alzheimer's disease (Polvikoski et al., 2010).

Thus, although individual differences in WMH or microstructure significantly relate to cognitive performance in both cognitively normal and impaired oldest-old adults (see Section 4.2), these white matter metrics do not differentiate cognitive status subgroups in advanced age. This pattern may indicate that the contribution of white matter to cognitive dysfunction in clinically impaired oldest-old adults is somewhat modest or that the cognitive status subgroups are defined by additional factors not captured by the measures of cognitive performance (e.g., impaired activities of daily

living). Regardless, finding comparable WMH accumulation (De Leeuw et al., 2001; Kawas et al., 2015) and microstructural degradation (Bennett et al., 2017; Merenstein et al., 2021a) in oldest-old adults with normal and impaired cognition may reflect higher brain reserve in the former group as they show preserved cognition in spite of white matter degradation. This interpretation would benefit from future work testing whether neural substrates beyond WMH and microstructure (e.g., functional activity and connectivity, larger brain volumes, low levels of amyloid-beta plaques) capture similar patterns of brain reserve that differ between these cognitive status subgroups in advanced age.

5. Functional MRI studies

5.1 Brain and neurocognitive aging in the oldest-old

Beyond the large number of structural studies whose samples extend into advanced age, there are also eight fMRI studies that have been conducted in oldest-old adults. Most task-related fMRI studies report decreased BOLD activity into advanced age that is independent of preserved or impaired performance, whereas resting-state fMRI studies find a mixture of age-related decreases (default mode) and increases (frontoparietal, motor) in functional connectivity. The literature supporting these findings is described below and summarized in Table 11.

Two studies compared BOLD activity between younger-old and oldest-old adults during recognition memory performance, with both controlling for age-related differences in whole brain volume (Beeri et al., 2011; Wang et al., 2009). When oldest-old adults had poorer memory performance than younger-old adults, it was accompanied

by less activity in hippocampal, temporal, and parietal regions, but comparable activity in frontal cortex (Beeri et al., 2011). When matching younger-old and oldest-old adults on memory performance, results similarly revealed age-related decreases in medial parietal activity but comparable activity in frontal and lateral parietal regions (Wang et al., 2009).

Other studies have examined BOLD activity across age groups as a function of task demands. One study compared oldest-old to younger adults who performed an executive control task, in which participants executed a motor response to a target stimulus that was preceded by a congruent (low load) or incongruent (high load) cue (Rosano et al., 2005a). Across load conditions, the oldest-old had similarly high accuracy levels as younger adults, but lower activity in the dorsolateral prefrontal and posterior parietal cortices. However, both age groups showed increased recruitment of these same regions for the high versus low load condition, and oldest-old adults with the greatest load-related parietal activity had the best performance. Another study compared adults across the lifespan (ages 20-89 years) during performance of a semantic judgment task, where participants made "living" versus "nonliving" judgments to words that were more (high load) or less (low load) ambiguous (Kennedy et al., 2015). Results also revealed similarly high accuracy levels across age groups, but performance was instead accompanied by decreased recruitment of frontal, temporal, and parietal regions at higher versus lower task loads, especially within the oldest-old subgroup (ages 80+ years).

Whereas the aforementioned fMRI studies focused on BOLD activity during performance of a task, at least two studies examined patterns of synchronous activity between regions while participants rested (i.e., functional connectivity). Across the older

adult lifespan, age-related differences were seen in connectivity of the default mode network, such that older adults had lower connectivity between regions such as the medial prefrontal cortex, posterior cingulate, and precuneus (Jiang et al., 2020; Li et al., 2020). The cross-sectional study also found greater bilateral frontoparietal connectivity that predicted better visuospatial performance for the oldest-old (Jiang et al., 2020), whereas the longitudinal study observed age-related increases in connectivity between the insula and supplementary motor area, with precuneus connectivity relating to changes in general cognitive performance (Li et al., 2020). Results of both studies were independent of whole brain volume and comparable to findings within younger-old and oldest-old adults with Alzheimer's disease (e.g., in the default mode network; Prawiroharjo et al., 2020), suggesting that they are not driven by cognitive dysfunction.

In summary, the task-related findings differ from the age-related increases in BOLD activity typically seen in high-performing younger-old adults, as well as the relatively consistent increases in BOLD activity as a function of task demands in younger age groups, and therefore contrast with compensation theories (Cabeza et al., 2018; Grady, 2008). They also differ from brain maintenance, which would have instead predicted similar BOLD activity and comparable cognitive performance in oldest-old and younger groups. To some degree, these interpretations depend on the reference group, as differences in the oldest-old were more widespread when compared to younger adults (Kennedy et al., 2015; Rosano et al., 2005a) than younger-old adults (Beeri et al., 2011; Wang et al., 2009). Whereas compensatory fMRI activity is commonly attributed to an increase in neural activity in younger-old adults who perform as well as younger adults,

some have proposed that compensatory activity follows an inverted U-shaped pattern across the entire adult lifespan (Cabeza and Dennis, 2014; Scheller et al., 2014). Such a pattern could be roughly approximated using both younger and younger-old comparison groups, which may reveal comparable neural activity in younger and high performing oldest-old adults, both of which differ from the increased activity seen in high performing younger-old adults. However, a fuller characterization of this U-shaped function will require a lifespan sample.

Given the relatively smaller fMRI literature, it remains somewhat unclear whether decreased BOLD activity reflects a maximization of neural resources in oldest-old adults (Reuter-Lorenz and Cappell, 2008) or whether they have higher brain reserve that protects against the effects of atrophy (Barulli and Stern, 2013). The latter would allow for efficient engagement of neural networks, which was supported by resting state studies finding stronger connectivity in the oldest-old (Jiang et al., 2020; Li et al., 2020). Ultimately, additional fMRI studies across the entire lifespan are needed to tease apart these possibilities, especially those using tasks with varied cognitive demands to prevent ceiling (younger adults) and floor (oldest-old adults) effects or allow age groups to be matched on performance (Wang et al., 2009).

5.2 Cognitive status subgroups in the oldest-old

Only one study examined BOLD activity between cognitive status subgroups in advanced age, which is summarized in Table 11. During performance of the same executive control task described above (Rosano et al., 2005b), greater activity was seen in dorsolateral prefrontal and posterior parietal cortices for oldest-old adults with impaired

versus normal cognition. Because there were no group differences in performance, it suggests that this response was compensatory. Thus, relative to cognitively normal younger-old and oldest-old adults, cognitively impaired oldest-old adults appear to show compensatory activity in parietal, not just frontal, regions.

6. Other MRI modalities

Beyond the select MRI modalities reviewed above, at least two studies examined the extent to which certain genotypes contributed to brain or neurocognitive aging in younger-old and oldest-old adults (Papenberg et al., 2015; Stickel et al., 2018). Two genes of particular interest are COMT (Catechol-O-Methyltransferase), which is implicated in neuromodulation of the prefrontal cortex and executive functions, and KIBRA, which is named for its role in producing proteins expressed in the kidneys and brain and has been implicated in episodic memory. Across studies, only oldest-old adults with the more favorable allele combination for COMT (Papenberg et al., 2015) or KIBRA (Strickel et al, 2018) had better prefrontal white matter microstructure or greater frontal and occipital volume, respectively. Having desirable allele combinations may therefore be a mechanism by which cognitively normal oldest-old adults maintain brain structure in advanced age.

Susceptibility-weighted imaging is another MRI modality of interest given its sensitivity to iron, which is known to accumulation with age and is thought to contribute to neurodegeneration via inflammation (Venkatesh et al., 2021; Zecca et al., 2004). Age-related increases in iron have been observed in oldest-old adults within the putamen (van Bergen et al., 2018), a subcortical structure known to gradually accumulate iron across

the younger adult lifespan (Hallgren and Sourander, 1958). However, this same study reported significantly less iron accumulation for oldest-old than younger-old cognitively normal adults in frontal, parietal, and temporal cortices (van Bergen et al., 2018). Intriguingly, because cortical iron loads are relatively low up until midlife and then increase across older adulthood (Acosta-Cabronero et al., 2016; Zecca et al., 2004), this cannot explain why a sample limited to older adults would paradoxically find age-related decreases in iron for cognitively normal oldest-old adults (van Bergen et al., 2018). Instead, minimal cortical iron accumulation may be a marker of sustained cognitive functioning in the ninth and tenth decades of life, which has implications for brain maintenance theory.

7. Methodological Considerations

General methodological constraints when conducting research on the oldest-old have been reviewed elsewhere. For example, the oldest-old are often extremely frail, making it difficult for them to travel to and navigate university testing sites (Rosa et al., 2020). There is also a strong sampling bias for oldest-old adults that are female, Non-Hispanic Whites, and have high educational attainment (Gardner et al., 2013; Poon et al., 2007). Here, we will discuss five additional methodological considerations specific to conducting neuroimaging research in the oldest-old: feasibility, vascular disease, iron accumulation, the presence of multiple pathologies, and the choice of reference group.

7.1 Feasibility

A potential limitation to obtaining MRI data in the oldest-old is their heightened frailty and the need for participants to lay in the supine position for an extended period.

Comfort can be maximized by using head padding, blankets, and leg cushions, and one study indeed reported similar overall comfort levels during MRI scanning (up to 1 hour) for younger-old and oldest-old participants (Wollman et al., 2004). However, the same study did find that the oldest-old were more bothered by MRI scanner noise, long scan times, and laying down. Researchers therefore need to weight the benefits of a shorter scan time (e.g., participant satisfaction, better data quality from less motion) with the cost of potentially reducing the number or resolution of scans. They might also wish to consider splitting higher-resolution acquisition sequences into multiple sessions, although this introduces the potential cost of losing data due to attrition.

Assuming researchers have access to well-characterized oldest-old populations that are interested and able to participate in research, feasibility then shifts to decisions about which MRI modalities to acquire. Structural MRI scans place minimal demands on participants beyond those for safely being scanned (e.g., not home bound, no metal, ability to lay supine). In contrast, task-related fMRI scans may be hampered by cognitive and physical (e.g., arthritis, vision and/or hearing problems) conditions that makes it difficult to understand task instructions and respond to stimuli via MR-compatible button-box. Researchers might therefore consider using extensive practice trials before entering the scanner and increasing the response time windows when asking oldest-old adults to perform cognitive tasks in the scanner. Functional MRI data also requires longer scan times as there are several structural images that are also needed for preprocessing (e.g., registration, region of interest, tissue segmentation). Nonetheless, these types of studies are crucial for understanding brain aging in the oldest-old and could be made

possible via large-scale, open access datasets, such as the Lifespan Human Connectome Project Aging (Bookheimer et al., 2019).

An alternative neuroimaging approach to study brain activity in the oldest-old is functional near-infrared spectroscopy (fNIRS), which uses near-infrared light to assess hemodynamic activity. One previous study used a portable fNIRS device to study a community-based sample of oldest-old adults at their personal residences, finding significant frontal activity during executive function performance that positively correlated with age (Huppert et al., 2017). This approach cannot fully replace fMRI, however, because it is limited to recording signals from cortical regions near the skull and cannot detect signals from deeper brain regions that are especially affected by advanced age, such as the hippocampus.

7.2 Effects of vascular disease

Another notable consideration when conducting MRI research on the oldest-old is the increased prevalence of vascular disease in advanced age, which accounts for some variance in cognitive decline (Rosa et al., 2020). Cardiovascular damage caused by small vessel disease and (micro)infarcts appears as hyperintensities on MR images (Wardlaw et al., 2015), thereby resulting in a decreased gray to white matter intensity ratio as age increases (Salat et al., 2009). This lack of differentiation between tissue types may lead to decreased precision of automated segmentation algorithms and registration pipelines used in MRI studies, affecting regional estimates for oldest-old relative to younger-old adults. Registration procedures based on white, rather than gray, matter boundaries may be more robust to pathologies and artifacts in MRI data of the oldest-old (Greve and Fischl, 2009).

Because the BOLD response indirectly measures neural activity as the ratio of oxygenated to deoxygenated blood, age-related vascular damage to the capillary beds feeding neural systems should also be considered when acquiring and interpreting fMRI data in the oldest-old (Kannurpatti et al., 2010; West et al., 2019). This vascular damage leads to a decreased ability to regulate neuronal homeostasis and energy demands, known as neurovascular coupling (Tarantini et al., 2017). Although the effects of age on neurovascular coupling do not appear to directly affect BOLD activity in younger-old adults (e.g., Grinband et al., 2017), this has not yet been tested in oldest-old adults. Future studies could estimate cardiovascular contributions to BOLD activity in advanced age (e.g., a breath holding task), although this will come at the expense of a slightly longer scanning protocol (Kannurpatti et al., 2010).

7.3 Accumulation of iron

Iron accumulation in the aging brain should also be considered as it may have a larger effect on the MR signal in oldest-old than younger-old adults. Specifically, the presence of iron can attenuate the MR signal at acquisition (Haacke et al., 2005) and influence measures of brain structure and function across regions that differentially accumulate iron across the lifespan (Hallgren and Sourander, 1958). Neuroimaging studies comparing younger-old and oldest-old adults may therefore be more accurate in regions that exhibit minimal (e.g., hippocampus) or gradual accumulation of moderate amounts of iron throughout the lifespan (e.g., caudate, putamen) compared to regions that accumulate large amounts of iron by early adulthood (e.g., globus pallidum). Importantly, quantitative susceptibility mapping sequences can be used to estimate iron burden so that

the effect of iron on the MR signal can be statistically accounted for (Ruetten et al., 2019).

7.4 Multiple pathologies

Another consideration is that the oldest-old may represent a distinct pathophysiological population, leading to multiple or even different neurobiological substrates contributing to a given MRI measure. Specifically, numerous dementia-related pathologies (e.g., amyloid-beta plaques, neurofibrillary tangles) are common in advanced age, even in individuals with normal cognition (Kawas et al., 2015; Yang et al., 2013). Because the high prevalence of dementia-related pathology in the oldest-old does not always manifest as observable cognitive impairment, the distinction between normal and disease-related brain aging is less clear compared to younger-old adults. To ensure generalizability of future studies to this entire population, special care should be taken to recruit well-characterized oldest-old adults both with and without cognitive impairment or dementia, as well as to include measures of Alzheimer's disease risk factors (e.g., APOE genotype) and pathology (e.g., amyloid-beta) when possible.

7.5 Reference group

Finally, an open question is whether the reference group for the oldest-old (80+) should be younger (20-30s) or younger-old (~55-80) adults. Younger adults would be analogous to the reference group used in studies of younger-old adults and could therefore detect comparable age effects, but could miss age effects that are unique to oldest-old relative to younger-old adults. In contrast, because younger-old adults have already experienced some of the deleterious effects of brain aging, comparisons would

only be sensitive to advanced age effects of sufficient magnitude, which may be underestimated. As such, future MRI studies disaggregating their results across each of these age groups will be fundamental to obtaining a more holistic view of advanced brain and cognitive aging (e.g., testing the proposed U-shaped function of compensatory activity in relation to age; Cabeza and Dennis, 2014).

8. Future Directions

8.1 Beyond brain macrostructure

Prior MRI studies in the oldest-old have largely focused on volumetry, WMH, and traditional DTI-derived measures of microstructure, which may be due in part to the ease of acquiring these data using clinical scanners. Going forward, theories of neurocognitive aging will benefit from studies assessing the effect of advanced age on other neural substrates. For example, future work using more advanced multi-shell diffusion imaging data acquisition and analyses (e.g., neurite orientation, density, and dispersion index, NODDI; Zhang et al., 2012) may better capture the multifaceted effects of brain aging in the oldest-old (Reas et al., 2021). Future studies might also consider prioritizing the collection of task-related fMRI data in this age group, as less is known about the functional substrates supporting cognitive performance in advanced age.

8.2 Multimodal imaging

Extant neurocognitive aging theories would also benefit from studies assessing interactions among multiple neuroimaging markers in advanced age as the majority of the literature reviewed here focused on a single imaging modality. One multimodal study found hippocampus atrophy, brain-wide WMH, and beta-amyloid accumulation in oldest-

old adults, but these measures were not correlated with each other (Lopez et al., 2014). Further evidence that they may be sensitive to different neural substrates is that each MRI measure was uniquely associated with cognitive status (Lopez et al., 2014) and individual differences in cognitive performance (Legdeur et al., 2020) in the oldest-old. Yet this interpretation would benefit from replication across age groups and brain regions. Other multi-modal approaches could examine relationships between brain structure and function in advanced age. To this end, the fMRI studies reviewed above were able to demonstrate that patterns of neural activity were independent of whole brain volume (Beeri et al., 2011; Jiang et al., 2020; Li et al., 2020; Wang et al., 2009). Future work combining DTI and fMRI could test whether decreased BOLD activity in oldest-old adults is instead driven by microstructural degradation of the white matter pathways connecting gray matter regions (Salat, 2011).

8.3 Neuroimaging-neuropathology associations

Given their advanced age, the oldest-old present a unique opportunity to acquire *in vivo* neuroimaging data and *ex vivo* pathological data in the same individuals. Several efforts are already underway to collect these data in advanced age, including The 90+ Study (Kawas and Corrada, 2006). Such datasets will be invaluable for validating neuroimaging markers (e.g., tissue volume, WMH, iron content, myelin content) against underlying neural substrates (e.g., loss or shrinkage of neurons or their processes, demyelination, perivascular space expansion, white matter disease, vascular damage). These data will also be vital for differentiating normal from pathological brain aging, such as whether the effects of advanced age on medial temporal and posterior brain

structure are driven by different amounts or types of pathologies in individuals across cognitive status subgroups.

9. Conclusion

Determining whether advanced age differentially affects MRI markers of brain and neurocognitive aging is crucial because previous neuroimaging research in younger-old adults may not generalize to individuals across the older adult lifespan. The current review supports the notion that there is regional variation in the magnitude of brain aging, such that frontal regions remain vulnerable across the older adult lifespan, whereas medial temporal and posterior regions become more vulnerable in the oldest-old. This review also found little support for compensation theories in the oldest-old, which differs from the large literature in younger-old adults, although this conclusion was based on very few fMRI studies. Nonetheless, our review did reveal strong support for the notion that both brain maintenance and brain reserve can explain sustained cognitive functioning in advanced age. In summary, older adults who reach the eighth through tenth decades of life exhibit different cognitive and neural profiles than the 60- or 70-year-olds represented in most previous MRI aging research (Figure 1) and these advanced age-related differences should be reflected in re-evaluations of current neurocognitive theories of aging.

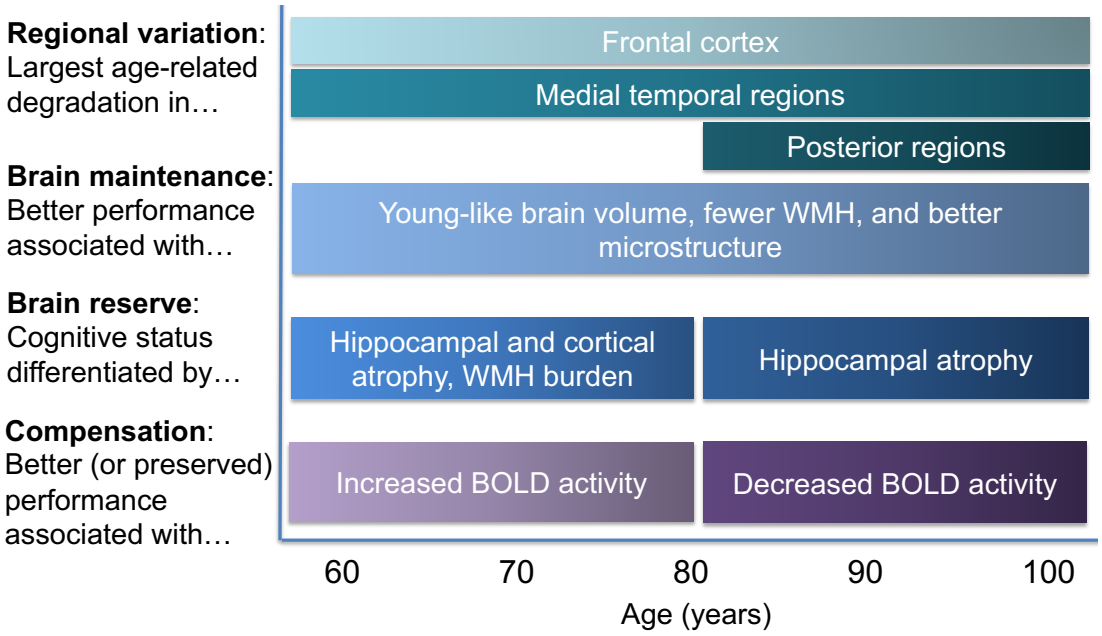

Figure 6. Neuroimaging patterns relevant to each neurocognitive aging theory reviewed here (left) are presented separately for younger-old (ages < 80 years) and oldest-old (80+ years) adults. Brain maintenance captures similar effects across the older adult lifespan, whereas oldest-old adults exhibit different patterns of regional variation, brain reserve, and functional compensation. WMH = white matter hyperintensities, BOLD = blood-oxygenation-level-dependent.

Table 8. Summary of structural studies examining brain aging.

Author (year)	Sample age (*n*)	Structural Modality	Age Effect(s) Frontal	MTL	Posterior	Whole brain
Volumetry & Morphometry						
Yang et al. (2016a)	71-103 (277)	Volume	-	- -	-	-
		Cortical thickness	-	- -	-	
Tang et al. (2021)	76-103 (290)	Sulcal width	-	-	-	
Li et al. (2020)	M=82 (34)	Cortical thickness	-	-		
Van Bergen et al. (2018)	55-96 (80)	Volume		o, -	-	
Mueller et al. (1998)	65-95 (46)	Volume	o	-	o	-
Brickman et al. (2008)	M=80 (769)	Volume		-		-
Salat et al. (1999)	65-95 (66)	Volume	-			
White matter hyperintensities & Microstructure						
Brickman et al. (2008)	M=80 (769)	WMH				-
Bennett et al. (2017)	90-103 (94)	FA, MD, AD, RD	o	-	- -	
Piguet et al. (2003)	81-97 (114)	WMH	-	-	- -	
Yang et al. (2016a)	71-103 (277)	WMH	-	-	-	-
Lövdén et al. (2013)	60-87 (260)	FA, MD	-	-	-	
Merenstein et al. (2021)	65-98 (108)	FA, AD, RD	-	- -	-	
Lövdén et al. (2014)	81-103 (563)	Δ FA, Δ MD	-		-	
Polvikoski et al. (2010)	85-104 (132)	WMH	-			

Notes. For each structural modality and brain region, symbols indicate observations of worse brain structure with age (-; i.e., smaller volume, more white matter hyperintensities [WMH], higher diffusivity), a larger negative effect of age in one region relative to other regions (- -), or no significant effect of age (o). Volumetry and morphometry studies are sorted by age effects in the medial temporal lobe (MTL). WMH and microstructure studies are sorted by age effects in the frontal lobe. FA = fractional anisotropy, MD = mean diffusivity, AD = axial diffusivity, RD = radial diffusivity, Δ = longitudinal change with age.

Table 9. Summary of structural MRI studies examining neurocognitive aging.

Author (year)	Sample age (*n*)	Structural modality	Cognitive domain(s)	Relationship to Cognition			
				Frontal	MTL	Posterior	Whole brain
Volumetry & Morphometry							
Carmichael et al. (2012)	60-95 (307)	Volume	Δ Episodic memory				-
Legdeur et al. (2019)	M=94.3 (171)	Δ Volume	Δ Episodic memory		-		
Pelkmans et al. (2021)	88-102 (57)	Volume	Δ Episodic memory		-		
Pelkmans et al. (2021)	88-102 (57)	Cortical thickness	Δ Episodic memory	-	-		
Eguchi et al. (2019)	96-99 (10)	Volume	Episodic memory		+		
Langnes et al. (2020)	4-93 (1,790)	Volume	Episodic memory		+		
Legdeur et al. (2020)	M=92.4 (122)	Volume	Episodic memory		+		
Pelkmans et al. (2021)	88-102 (57)	Volume	Processing speed		+		
Legdeur et al. (2020)	M=92.4 (122)	Volume	Processing speed		+		
Legdeur et al. (2019)	M=94.3 (171)	Δ Volume	Δ General cognition		-		
White matter hyperintensities & Microstructure							
Pelkmans et al. (2021)	88-102 (57)	WMH	Δ Episodic memory				-
Legdeur et al. (2020)	M=92.4 (122)	WMH	Episodic memory				+
Langnes et al. (2020)	4-93 (1,790)	MD	Episodic memory		+		
Merenstein et al. (2021)	65-98 (108)	FA, AD	Episodic memory		+		
Reas et al. (2021)	56-99 (147)	MDI	Episodic memory	+	+	+	
Piguet et al. (2003)	81-97 (114)	WMH	Episodic memory	+			
Pelkmans et al. (2021)	88-102 (57)	WMH	Processing speed				+
Liu et al. (2015)	79-89 (283)	WMH, MD	Processing speed				+
Venkatraman et al. (2011)	M=83 (272)	FA, MD	Processing speed				+
Legdeur et al. (2020)	M=92.4 (122)	WMH	Processing speed				+
Laukka et al. (2013)	60-87 (253)	FA, MD	Processing speed	+	+	+	
Rosano et al. (2015)	M=83 (311)	WMH, FA	Processing speed	+		+	
Haynes et al. (2017)	70-90 (526)	WMH	Processing speed	+			
Lövdén et al. (2014)	81-103 (563)	Δ FA, Δ MD	Δ Processing speed	-			
Legdeur et al. (2019)	M=94.3 (171)	Δ WMH	Δ General cognition				-
Carmichael et al. (2012)	60-95 (307)	WMH	Δ Semantic memory				-
Carmichael et al. (2012)	60-95 (307)	WMH	Δ Executive function				-

Notes. For each structural modality and brain region, symbols indicate positive (+) or negative (-) associations between brain structure (i.e., smaller volume, more white matter hyperintensities [WMH], higher diffusivity) and cognitive performance. Processing speed was reverse coded with higher values representing better performance. All studies are sorted by the cognitive domain examined. FA = fractional anisotropy, MD = mean diffusivity, AD = axial diffusivity, Δ = longitudinal change, MTL = medial temporal lobe, MDI = multicompartment diffusion imaging.

Table 10. Summary of structural MRI studies examining cognitive status subgroups.

Author (year)	Sample age (*n*)	Structural modality	Effect of Cognitive Status							
			Frontal		MTL		Posterior		Whole brain	
			YO	OO	YO	OO	YO	OO	YO	OO
Volumetry & Morphometry										
Stricker et al. (2011)	60-91 (230)	Cortical thickness			+	o	+	o		
Barkhof et al. (2007)	85-105 (132)	Volume				+				
Gosche et al. (2002)	87-93 (56)	Volume				+				
Lopez et al. (2014)	72-96 (183)	Volume			+	+				
Yang et al. (2016b)	71-103 (244)	Volume	+	+	+	+	+	+		
Holland et al. (2012)	65-90 (723)	Volume			+	+	+	o	+	o
Rosano et al. (2012)	M=83 (258)	Δ Volume				-				
White matter hyperintensities & Microstructure										
Rosano et al. (2012)	M=83 (258)	Δ MD		-				-		
Zamboni et al. (2019)	20-102 (566)	WMH, FA, MD	+	o					+	o
Polvikoski et al. (2010)	85-104 (132)	WMH		+						
Tanskanen et al. (2013)	85-105 (123)	WMH								o
Yang et al. (2016b)	71-103 (244)	WMH							o	o
Rosano et al. (2012)	M=83 (258)	Δ WMH								o

Notes. For each structural modality and brain region, symbols indicate observations of better (+), fewer changes (-), or no difference (o) in brain structure (i.e., smaller volume, more white matter hyperintensities [WMH], higher diffusivity for cognitively normal younger-old (YO) and/or oldest-old (OO) age groups relative to those with cognitive impairment or Alzheimer's disease and other dementias. Volumetry and morphometry studies are sorted by age effects in the medial temporal lobe (MTL). WMH and microstructure studies are sorted by age effects in the frontal lobe followed by the whole brain. FA = fractional anisotropy, MD = mean diffusivity, Δ = longitudinal change.

Table 11. Summary of functional MRI studies.

Author (year)	Sample age (*n*)	Cognitive domain	Effect of Age on BOLD Activity		
			Frontal	MTL	Posterior
Task-related fMRI					
Beeri et al. (2011)	70-90+ (29)	Recognition memory	o	-	-
Wang et al. (2009)	64-96 (34)	Recognition memory	o	o	-
Rosano et al. (2005a)	12-82+ (28)	Executive control	-		-
Rosano et al. (2005b)	M=80-82 (16)	Executive control	$+^{CI > CN}$		$+^{CI > CN}$
Kennedy et al. (2015)	20-89 (316)	Semantic judgments	-	-	-
Resting state fMRI			Default mode	Frontoparietal	Motor
Prawiroharjo et al. (2020)	65-80+ (44)	Recall memory	+		+
Jiang et al. (2020)	76-103 (104)	Visuospatial task	-	+	+
Li et al. (2020)	M=82 (34)	Δ General cognition	+		+

Notes. For each functional modality and brain region (task-related) or network (resting state), symbols indicate positive (+), negative (-), or non-significant (o) associations between age and BOLD activity. All studies are sorted by the cognitive domain examined. Superscripts indicate that the effect was seen for cognitively impaired (CI) versus normal (CN) subgroups. Δ = longitudinal change.

General Conclusion

This dissertation furthered our understanding of neurocognitive aging across the older adult lifespan by examining the effects of advanced age on MRI markers of brain aging and their relation to cognition. Two studies using diffusion-weighted imaging demonstrated that advanced age negatively affects white matter microstructure (Chapter 1) and that this in turn negatively affects episodic memory (Chapter 1) and associative learning (Chapter 2) abilities into the 10th decade of life. An integrative review of the literature (Chapter 3) then summarized extant MRI studies in this advanced age group and interpreted their findings within the context of modern neurocognitive aging theories. Together, this body of work supports the notion that age-related differences in white matter microstructure (among other neural substrates) affect cognitive functioning across the entire older adult lifespan and suggests that modern theoretical accounts may need to consider the impact of oldest-old adults on the accuracy of their predictions.

Using traditional DTI, Chapter 1 found that age effects on white matter microstructure (e.g., demyelination, axonal shrinkage, decreased fiber density) and episodic memory are magnified in oldest-old (ages 90+) relative to younger-old (ages 65-89) adults. The largest age effects were observed in medial temporal memory-related white matter regions, and all results were independent of cognitive impairment no dementia (CIND) diagnoses in the oldest-old. Thus, exacerbated white matter degradation cannot solely be explained by the increased risk of developing dementia in this advanced age group. Moreover, in support of the cortical disconnection hypothesis (Bartzokis,

2004; O'Sullivan et al., 2001), the microstructure of medial temporal memory-related white matter regions mediated the negative effect of age on two different measures of memory performance. Together, these findings indicate that white matter deteriorates in a more accelerated manner towards the end of the older adult lifespan and remains crucial for facilitating memory-related neural signals. Relative to traditional diffusion tensor approaches, however, more advanced multicompartment diffusion imaging techniques may better capture the multifaceted effects of advanced brain aging. Because this study assessed memory using a more standard list learning neuropsychological test, it is also important to demonstrate the specificity of advanced white matter aging to more precise cognitive measures.

These limitations inspired the follow-up study presented in Chapter 2, which examined the relation between multicompartment diffusion imaging measures of microstructure and performance on a laboratory-based associative learning task within oldest-old adults. Results indicated significant behavioral evidence of associative learning, with better performance seen during later stages of the task. Oldest-old adults with the best learning performance also had better microstructure of the anatomical pathways connecting prefrontal and striatal regions, which have been implicated in associative learning by functional MRI studies of younger age groups (Merenstein et al., 2021b; Persson et al., 2020; Simon et al., 2012). Similar to Chapter 1, results were independent of CIND diagnoses, suggesting that associative learning abilities are preserved into the 10th decade of life and can be attributed to normal age- and individual-related differences in the microstructure of fronto-striatal pathways. Because this was the

first study to examine associative learning abilities and its white matter correlates in advanced age, future studies are needed to replicate these effects within larger samples of nonagenarians and across younger-old and oldest-old adults.

Toward the broader goal of identifying robust patterns of brain and cognitive aging in the oldest-old, Chapter 3 reviewed the findings from prior MRI studies examining advanced neurocognitive aging and whether they are comparable to findings reported within younger-old adults, as would be predicted by theories of neurocognitive aging. Results revealed that oldest-old adults exhibit different regional patterns of brain aging and minimal evidence of compensatory neural activity than is typically seen in younger-old adults, although there was strong support for brain maintenance and reserve theories in advanced age. Thus, while some theoretical accounts accurately capture patterns of neurocognitive aging across the entire older adult lifespan, others may need to be adapted to account for the more heterogenous cognitive and neural profiles seen during the eighth through 10th decades of life.

In closing, this dissertation provided one of the initial characterizations of advanced neurocognitive aging, thereby laying important groundwork for future MRI studies examining brain and cognitive aging within the oldest-old. Finding that poorer white matter microstructure predicted poorer cognitive performance (episodic memory, associative learning) in a sample of very old adults suggests that age-related white matter degradation interferes with efficient neurotransmission and ultimately contributes to cognitive dysfunction, as predicted by the cortical disconnection hypothesis (Bennett and Madden, 2014; O'Sullivan et al., 2001). However, other theoretical accounts may need to

be modified to account for the unique signatures of neurocognitive aging observed toward the end of the lifespan. Furthering our understanding of the relation between cognitive aging and brain aging in this advanced age group is timely as nearly 1 in 20 individuals will reach age 85 by the year 2050 (Ortman et al., 2014).

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Appendix A

Supplementary Table 1. Linear and nonlinear relationships between age and white matter microstructure.

	Linear / nonlinear R^2		
White matter region	FA	AD	RD
Medial temporal fibers			
Fornix body	**0.30 / 0.30**	0.01 / 0.01	**0.34 / 0.34**
Fornix cres	**0.30 / 0.31**	0.01 / 0.01	**0.34 / 0.35**
Hippocampal cingulum	**0.27 / 0.28**	**0.09 / 0.09**	**0.33 / 0.34**
Uncinate fasc.	**0.17 / 0.17**	**0.09 / 0.09**	**0.29 / 0.29**
Callosal fibers			
Genu	**0.15 / 0.15**	**0.41 / 0.41**	**0.30 / 0.30**
Body	**0.13 / 0.13**	**0.13 / 0.12**	**0.22 / 0.23**
Splenium	**0.10 / 0.10**	*0.05 / 0.05*	**0.15 / 0.16**
Association fibers			
Superior cingulum	**0.24 / 0.25**	**0.09 / 0.08**	**0.36 / 0.37**
Sagittal stratum	**0.14 / 0.15**	**0.29 / 0.29**	**0.28 / 0.29**
External capsule	**0.24 / 0.24**	**0.20 / 0.19**	**0.35 / 0.35**
Superior fronto-occipito fasc.	*0.08 / 0.08*	**0.41 / 0.42**	**0.21 / 0.22**
Superior longitudinal fasc.	**0.09 / 0.09**	**0.37 / 0.38**	**0.23 / 0.24**
Projection/thalamic fibers			
Internal capsule	**0.10 / 0.10**	**0.19 / 0.19**	**0.20 / 0.20**
Posterior thalamic radiations	**0.24 / 0.24**	**0.17 / 0.16**	**0.30 / 0.31**
Corona radiata	**0.14 / 0.14**	**0.50 / 0.50**	**0.36 / 0.36**

Notes: Significant (bolded, Bonferroni corrected $p < 0.003$ for comparisons across 15 regions) or trending (italics, $p < 0.05$) coefficients of determination (R^2) values from linear regressions of age (linear) or age squared (nonlinear) 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 white matter region.

Appendix B

Associative Learning Performance

Evidence of IAL was assessed using separate repeated measures analyses of variance (ANOVAs) with Triplet Type (HF, LF) and Task Stage (1-5) modeled as within-person variables and mean accuracy or logarithmically transformed mean of median reaction time (to control for age-related slowing; Franco et al., 2021; Simon et al., 2010) as the dependent variable.

For accuracy, IAL was seen as a significant main effect of Triplet Type, $F(1, 21) = 5.35$, $p = 0.031$, indicating that participants were significantly more accurate to HF than LF triplets (Supplementary Figure 1 and Supplementary Table 2). General skill learning was seen as a significant main effect of Task Stage, $F(4, 84) = 12.34$, $p < 0.001$, with more accurate responses during Task Stages 2-5 than Task Stage 1 (Supplementary Figure 1 and Supplementary Table 2). The interaction was not significant, $p = 0.201$.

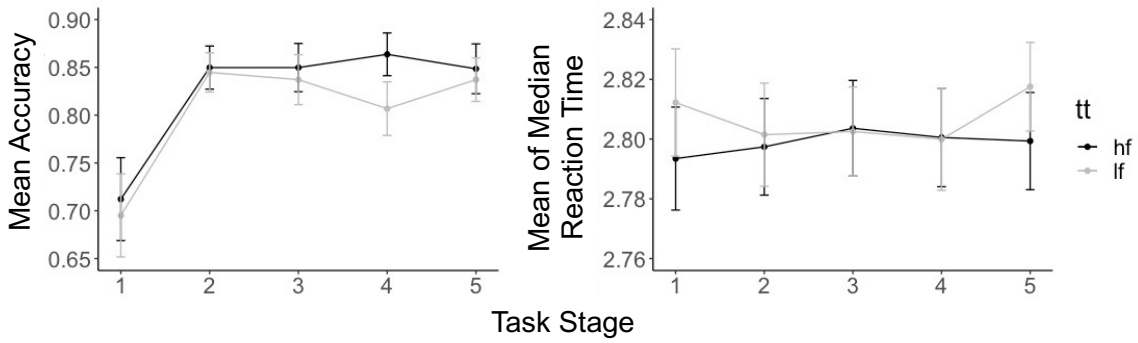
For reaction time, there were no significant effects, $p = 0.062$ (Supplementary Figure 1 and Supplementary Table 2).

When repeating the above ANOVAs with Cognitive Status (cognitively normal, CIND) as a covariate, results revealed no significant main effect of or interaction with Cognitive Status for either behavioral metric, ps > 0.231.

Supplementary Table 2. Associative learning performance.

	Accuracy			Mean of median reaction time		
	HF	LF	Difference	HF	LF	Difference
Stage 1	0.712 (0.203)	0.695 (0.203)	0.017 (0.094)	2.793 (0.081)	2.812 (0.084)	0.019 (0.062)
Stage 2	0.850 (0.106)	0.845 (0.096)	0.005 (0.097)	2.797 (0.076)	2.801 (0.081)	0.004 (0.027)
Stage 3	0.850 (0.118)	0.837 (0.122)	0.013 (0.066)	2.804 (0.075)	2.803 (0.070)	0.001 (0.024)
Stage 4	0.864 (0.105)	0.807 (0.131)	0.057 (0.085)	2.801 (0.077)	2.800 (0.080)	0.001 (0.018)
Stage 5	0.848 (0.122)	0.837 (0.107)	0.011 (0.060)	2.799 (0.076)	2.818 (0.070)	0.018 (0.027)
Average	0.845 (0.109)	0.824 (0.010)	0.021 (0.041)	2.799 (0.074)	2.805 (0.071)	0.006 (0.015)

Notes. All scores are presented as mean (standard deviation). Reaction times are logarithmically transformed.



Supplementary Figure 1. Behavioral results are displayed as a function of Task Stage and high (HF, black) or low (LF, gray) frequency Triplet Type (tt), separately for accuracy (left) and logarithmically transformed mean of median reaction times (right). Error bars represent standard error of the mean.