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Age-related differences in white matter microstructure measured by advanced diffusion MRI in healthy older adults at risk for Alzheimer's disease

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ABSTRACT

Neurite orientation dispersion and density imaging (NODDI) is an advanced diffusion imaging technique, which can detect more distinct microstructural features compared to conventional Diffusion Tensor Imaging (DTI). NODDI allows the signal to be divided into multiple water compartments and derive measures for orientation dispersion index (ODI), neurite density index (NDI) and volume fraction of isotropic diffusion compartment (FISO). This study aimed to investigate which diffusion metric—fractional anisotropy (FA), mean diffusivity (MD), NDI, ODI, or FISO—is most influenced by aging and reflects cognitive function in a population of healthy older adults at risk for Alzheimer's disease (AD). Age was significantly associated with all but one diffusion parameters and regions of interest. NDI and MD in the cingulate region adjacent to the cingulate cortex showed a significant association with a composite measure of Executive Function and was proven to partially mediate the relationship between aging and Executive Function decline. These results suggest that both DTI and NODDI parameters are sensitive to age-related differences in white matter regions vulnerable to aging, particularly among older adults at risk for AD.
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Introduction

Much of current Alzheimer's disease (AD) research is focused on the preclinical phase of the disease, where pathological changes are occurring, but no clinical symptoms have yet developed [19]. Because the pathological

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changes of AD can be present decades before the onset of symptoms, there is a need for robust biomarkers to detect these changes early on. Most commonly, AD is characterized by extracellular amyloid beta (Aβ) plaques and neurofibrillary tangles, however, white matter damage is also known to play a role in the pathophysiology and may present at early stages of the disease [32,33,62]. Much of the previous research in this area has been focused on structural magnetic resonance imaging (MRI), capturing atrophy and white matter lesions. However, many microstructural changes, such as axonal damage and disintegration, loss of neuronal cells, and myelin degradation have been shown to precede volumetric changes [29], highlighting the need for more sensitive techniques. In order to fully understand the pathophysiology of AD, it is imperative to understand and characterize the *in vivo* microstructural changes occurring in the white matter during healthy aging. An added challenge is determining the tools most suitable for the task.

Diffusion Tensor Imaging (DTI) has been widely used to study the impact of AD pathology on both white and gray matter microstructure in older adults at risk for AD, individuals with mild cognitive impairment (MCI), and AD patients [3,12,45,48,59,64]. DTI metrics are able to quantify the structural integrity of neural tissue *in vivo* by using the diffusion of water molecules to distinguish different microstructural environments. However, this technique is not without its limitations. Due to the simplicity of common tensor models, DTI lacks the specificity to disentangle distinct microstructural features of white and gray matter. For example, fractional anisotropy (FA), which is the most-widely studied DTI metric, could reflect changes in axonal density, diameter, or myelination, changes in fiber orientation, or partial volume effects [23,65].

In order to combat these shortcomings, more advanced diffusion imaging techniques and modeling approaches have been developed. Neurite orientation dispersion and density imaging (NODDI) is an advanced model which can be applied to multi-shell diffusion-weighted imaging, which divides the signal into three compartments: fast isotropic diffusion (e.g., cerebrospinal fluid (CSF)), anisotropic hindered diffusion (e.g., extracellular water), and highly restricted anisotropic diffusion (e.g., intra-axonal compartments) [73]. From these compartments, parameters such as neurite density index (NDI), orientation dispersion index (ODI), and volume fraction of the isotropic diffusion compartment (FISO) can be calculated. Regions with high ODI values are thought to reflect highly dispersed neurites (a term referring to both dendrites and axons) and complex cytoarchitecture, for example in the gray matter, while lower ODI values are more likely to correspond to more tightly organized structures, such as white matter tracts [20,24,73]. NDI, which is comprised of the fraction of water inside axons and dendrites, characterizes neurite density by restricted diffusion perpendicular to the neurites. NDI is expected to be high in normal white matter and lower in gray matter. NDI is also expected to decrease in regions of axonal thinning and degeneration [15,28]. Finally, FISO, which reflects the fraction of freely diffusing water is high in cerebrospinal fluid and low in white and gray matter.

NODDI metrics may provide a more specific characterization of white matter tissue microstructure, as compared to DTI [65]. One study comparing DTI and NODDI has found that while the two models are complementary, NODDI was able to more precisely discriminate regional differences in a clinical sample population [65]. In addition, the ability to model the free water compartment with NODDI provides a significant benefit by reducing partial volume effects, which are not explicitly considered in conventional DTI [49]. Furthermore, the measures of neurite density and orientation dispersion have been shown to correlate with histology [15,27,55,60,65,70]. Considering all of these potential benefits of NODDI, it is worth exploring whether the technique is better at analyzing more complex fiber architecture and provides more specificity to aging.

Since age is the primary risk factor for AD, the main goal of this study was to examine the effect of aging on white matter integrity across five key diffusion measurements (FA, MD, NDI, ODI, and FISO) in cognitively healthy late-middle-aged adults at risk for AD. We also aimed to investigate the link between diffusivity and cognitive functioning, specifically composite measures of Immediate Learning, Delayed Recall, and Executive Function. Analyses were performed using multivariate general linear models and mediation analysis to discern these relationships. We hypothesized that white matter MD, ODI, and FISO would increase with age, while FA and NDI would be reduced. We also expected that these diffusion changes would be reflected in a reduction of cognitive function with age.

Methods

Participants

Three hundred eighty-three late-middle-aged adults from the Wisconsin Registry for Alzheimer's Prevention (WRAP) [35,53] participated in this study. The WRAP is a cohort study of ~ 1500 middle-aged adults who are at increased risk for AD due to parental history of AD dementia. Participants were included in this study if they were cognitively unimpaired, underwent a Hybrid Diffusion Imaging (HYDI) MRI scan and completed a cognitive assessment within 2 years of the MRI scan (mean time difference = 0.387 ± 0.412 years, range = [0, 1.92]). It is worth noting that data from one hundred and six participants have been included in a previous publication by Merluzzi et al. [42]. Written consent was obtained from all participants prior to study procedures. All procedures were approved by the University of Wisconsin Health Science Institutional Review Board.

Image Acquisition and processing

MRI data were acquired using a General Electric 3 T MR750 scanner (Waukesha, WI) with an 8-channel head coil. Diffusion-weighted images (DWI) were acquired using a Hybrid Diffusion Imaging (HYDI) multi-shell spin-echo echo-planar imaging pulse sequence. Each dataset was acquired using one of three acquisitions. The parameters

for each acquisition are listed in Table 1. Acquisition 3 featured a reverse polar acquisition.

The DWI data were processed using the following sequence of procedures. Denoising [69] and Gibb's ringing correction [37] were performed using MRtrix3 [66], and motion and eddy current correction were performed using the *eddy* tool with outlier replacement [4] in FSL (v6.0.1) [34]. Brain tissue was identified using the Brain Extraction Tool [61] in FSL and brain masks were computed for each individual. Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps were derived by fitting a tensor at each voxel using Diffusion Imaging in Python [25]. Neurite Orientation Dispersion and Density Imaging (NODDI) parameter maps, NDI, ODI, and FISO, were calculated in Python using Accelerated Microstructure Imaging via Convex Optimization [17].

After the DTI and NODDI parameter maps were computed, an iteratively optimized population-specific template was generated from the individual-level FA maps using the antsMultivariateConstruction2.sh script in ANTs [5]. The regions of interest (ROIs) for this study were obtained from the Johns Hopkins University (JHU) ICBM-DTI-81 white matter atlas [46] provided in FSL. The JHU FA atlas was non-linearly registered to the population-specific template and for each of the subjects, the resulting transformation matrixes were then used to warp atlas-space ROIs into native diffusion space. To avoid partial volume effects from gray matter and CSF, each participant's diffusion map was multiplied by a white matter fraction map, which was generated using the *Atropos* segmentation tool [5]. For each participant, the mean metric value of voxels inside each ROI was calculated in the FA, MD, NDI, ODI, and FISO maps. Finally, neuroCombat [22] was used to harmonize the ROI data from different acquisitions separately for each metric using age and sex as covariates.

Four white matter ROIs were chosen due to their known vulnerability to aging and involvement in AD pathology: corpus callosum genu and splenium, and two regions of the cingulum bundle, cingulum adjacent to the cingulate cortex (cingulum-CC) and cingulum bundle projections to the hippocampus (cingulum-HC) [1,2,9,10,21,38,39,41,43,74]. These regions of interest are depicted in Fig. 1. To reduce multiple comparisons, the hemispheric structures were averaged into a single bilateral measure.

Cognitive assessments

All participants underwent a comprehensive battery of cognitive tests administered by a trained psychometrist [35]. Domain-specific composite scores were used as the outcomes for analysis as opposed to individual test scores in order to reduce measurement error and limit the potential Type I error associated with conducting multiple comparisons, thus improving statistical power. Composite scores have been shown to have less variability and stronger relationships with age and AD biomarkers compared to raw scores [18,40] and appear to be sensitive to early cognitive changes [44]. Three composite scores [13] were calculated by transforming raw test scores to z-scores using the means and standard deviations of the WRAP sample, and then averaging the z-scores. The composite scores are:

- Immediate Learning: Rey Auditory Verbal Learning Test (RAVLT) [56] (total trials 1–5), Wechsler Memory Scale-Revised Logical Memory subtest (WMS-R LM) [72] (immediate recall), Brief Visuospatial Memory Test (BVMT-R) [7] (immediate recall).
- Delayed Recall: RAVLT (long-delay recall), WMS-R LM (delayed recall), BVMT-R (delayed recall).
- Executive Function: Trail Making Test Part B (TMT B) [52] (total time to completion), Stroop Color-Word Test [67] Color-Word Interference (total items correctly completed in 120 s), Wechsler Adult Intelligence Scale-Revised (WAIS-R) [71] Digit Symbol Coding (total items correctly completed in 90 s). The z-score for TMT B was reversed prior to inclusion in the composite so that higher z-scores indicated better performance for all tests.

Statistical analysis

A multivariate general linear model that simultaneously tested the four white matter ROIs was used to determine which of the five diffusion parameters (i.e., FA, MD,

Table 1
HYDI acquisition parameters.

Parameter	Acquisition 1	Acquisition 2	Acquisition 3	
N	166	76	141	
B values (s/mm^2)	7 × b = 0	6 × b = 0	4 × b = 0	4 × b = 0
	6 × b = 300	9 × b = 500	9 × b = 300	7 × b = 300
	21 × b = 1200	18 × b = 800	15 × b = 1200	17 × b = 1200
	24 × b = 2700	36 × b = 2000	17 × b = 2700	15 × b = 2700
	24 × b = 4800		15 × b = 4800	17 × b = 4800
	50 × b = 7500		33 × b = 7600	31 × b = 7600
TR (ms)	6500	8575	3600	
TE (ms)	101.9	77	96.4	
FOV (mm)	256	256	240	
Zero filling	Yes	No	No	
Acquisition Matrix	128 × 128	128 × 128	96 × 96	
In-plane resolution (mm^2)	0.9375 × 0.9375	2.0000 × 2.0000	2.500 × 2.500	
Slice Thickness (mm)	3.0000	1.0000	2.5000	

Abbreviations: TR = repetition time; TE = echo time; FOV = field of view.

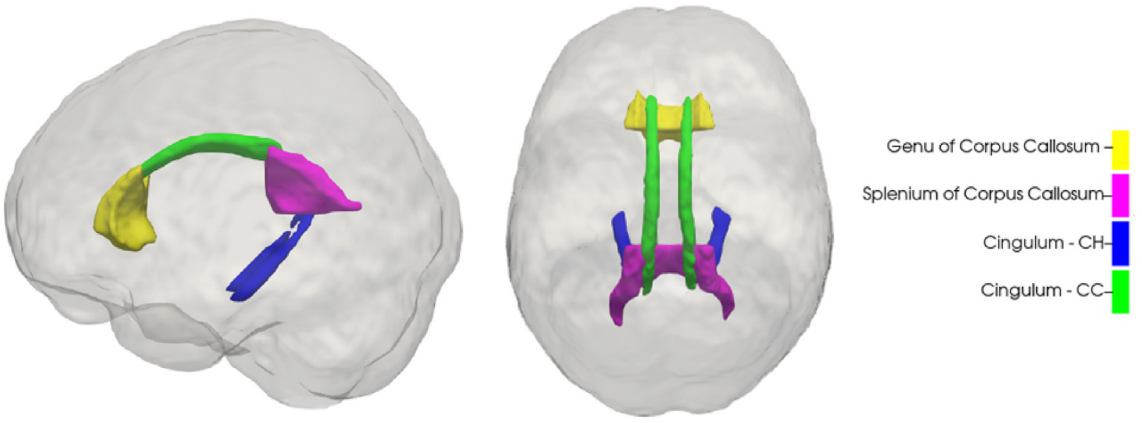

Fig. 1. Regions of interest. Diffusivity values were extracted from the regions of interest illustrated here: genu of corpus callosum (yellow), splenium of corpus callosum (magenta), cingulum bundle projections to the hippocampus (cingulum-CH) (blue), cingulum adjacent to the cingulate cortex (cingulum-CC) (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

NDI, ODI, and FISO) was most impacted by age, while controlling for biological sex and *APOE* ε4 genotype. Participants were considered *APOE* ε4 positive if they carried one or more ε4 alleles and *APOE* ε4 negative if no ε4 alleles were present. An additional general linear model was run with the inclusion of AD parental history as a covariate and another was run with cardiovascular risk as a covariate. Cardiovascular risk was indexed with the ASCVD (Atherosclerotic Cardiovascular Disease) risk score, which incorporates age, gender, race, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, treatment for high blood pressure, diabetes, and smoking [26]. The diffusion parameters that showed at least a medium Cohen's effect size (i.e., $f^2 \geq 0.15$) [14] association with age were then subsequently used in a general linear model to predict cognitive function. The same covariates were used as described above with the addition of education. An additional general linear model was performed to examine the association between age and cognitive function while controlling for biological sex, *APOE* ε4 genotype, and education. Lastly, a mediation analysis was performed to determine if the diffusion metrics mediated the effect of aging on cognition using the PROCESS macro v3.4 [31]. All $p < 0.05$ findings were considered significant. All statistical analyses were conducted in IBM SPSS v 25 (IBM Corp. Armonk, NY).

Results

Participant characteristics

Participant demographic data are presented in Table 2**.** Briefly, the sample was late-middle aged (mean age = 64.49 years, range = [45.40, 81.13]), mostly composed of women (67.1%), and highly educated (mean years of schooling = 16.67 years). Population average maps of FA, MD, NDI, ODI, and FISO are shown in Fig. 2. As expected, FA maps show higher intensity in white matter relative to gray matter and CSF, suggesting high tissue coherence (Fig. 2**a**). MD is higher in gray matter and CSF, while comparatively lower in white matter (Fig. 2**b**). White matter has higher intensity in NDI compared to gray matter indicating higher intra axonal volume fraction (Fig. 2**c**). ODI maps exhibit low intensity in the white matter, indicating lower dispersion (Fig. 2**d**). Finally, FISO is high in CSF and low in white and gray matter (Fig. 2**e**).

Table 2
Background characteristics of study participants.

Variable	Value
Age, mean years (std. dev)	64.49 (6.92)
Female, %	67.10
Education, mean years (std.dev)	16.67 (2.91)
APOE ε 4 carrier, %	35.50
AD Parental History, %	67.10
White, %	95.60

Abbreviations: *APOE* = Apolipoprotein E; AD = Alzheimer's disease.

Age and DWI

Associations between each microstructural measure and age were generally in the expected direction after controlling for sex and *APOE* ε4 genotype. The multivariate tests showed significant age associations with all five diffusion metrics: FA ($F(4,376) = 13.829$, $p < 0.001$), MD ($F(4,376) = 27.898$, $p < 0.001$), NDI ($F(4,376) = 19.019$, $p < 0.001$), ODI ($F(4,376) = 7.76$, $p < 0.001$) and FISO ($F(4,376) = 19.593$, $p < 0.001$). The individual ROI results from this analysis are summarized in Table 3**.** The addition of AD parental history as a covariate did not impact the results substantively. The addition of cardiovascular risk resulted in a decreased Cohen's effect size between age and diffusion metrics. However, the ROIs exhibiting the largest effect size did not change. After using the Bonferroni method to correct for multiple comparisons, all associations were significant with the exception of cingulum-CC ODI and FISO. Four associations exhibited medium Cohen's effect sizes: MD in the cingulum – CC and genu of corpus callosum and NDI in cingulum – CC and genu of corpus callosum. Scatter plots of these four associations

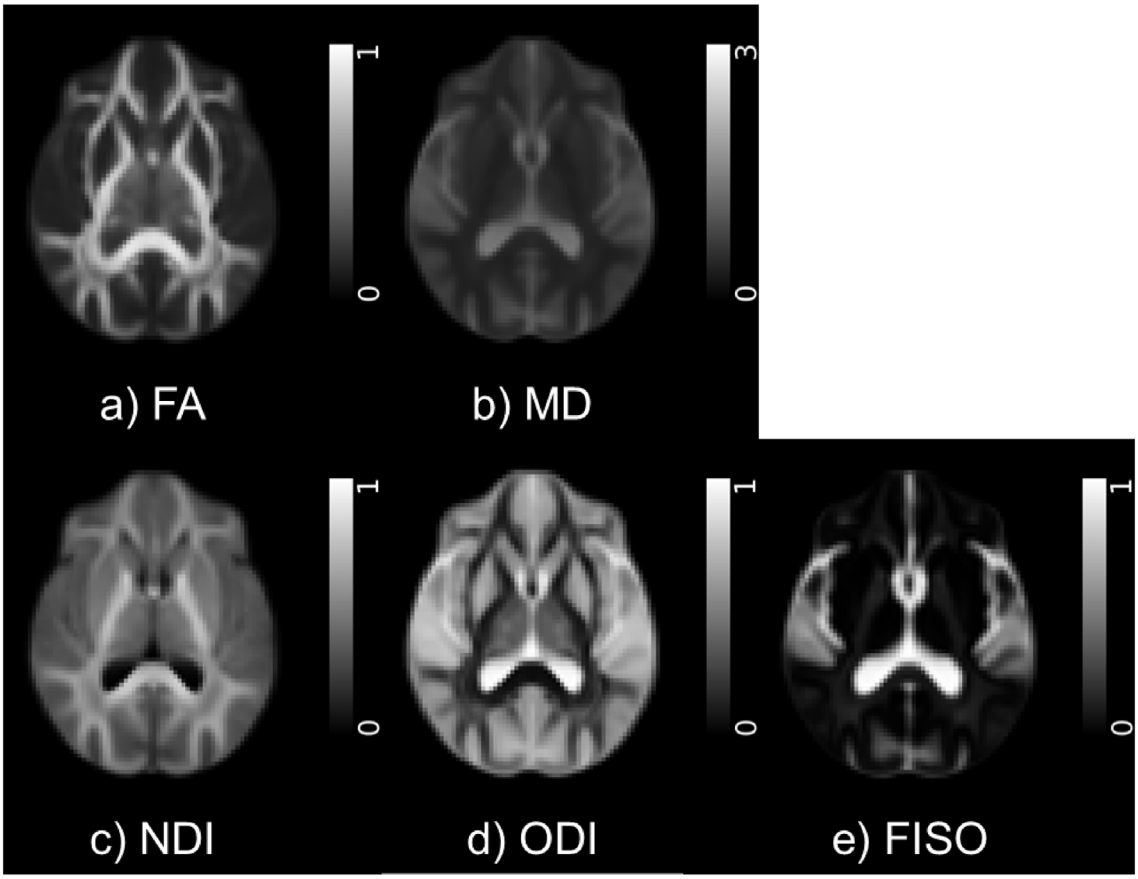

Fig. 2. Average diffusion maps. Population average maps of a) fractional anisotropy (FA), b) mean diffusivity (MD), c) neurite density (NDI), d) orientation dispersion index (ODI), and e) volume fraction of the isotropic diffusion compartment (FISO). MD is displayed in units of $\mu m^2/s$.

Table 3
Associations between age and diffusivity metrics.

Metric	Regions of Interest	B	Std. Error	Sig.	Cohen's Effect Size (f^2)
FA	Cingulum – CC	−0.001	0.000	p < 0.001	0.056
	Cingulum – CH	−0.001	0.000	p < 0.001	0.048
	Genu of corpus callosum	−0.002	0.000	p < 0.001	0.131
	Splenium of corpus callosum	−0.001	0.000	p < 0.001	0.041
MD	**Cingulum – CC**	**0.001**	**0.000**	**p < 0.001**	**0.212**
	Cingulum – CH	0.001	0.000	p < 0.001	0.149
	Genu of corpus callosum	**0.003**	**0.000**	**p < 0.001**	**0.205**
	Splenium of corpus callosum	0.002	0.000	p < 0.001	0.072
NDI	**Cingulum – CC**	**−0.002**	**0.000**	**p < 0.001**	**0.175**
	Cingulum – CH	−0.001	0.000	p < 0.001	0.058
	Genu of corpus callosum	**−0.003**	**0.000**	**p < 0.001**	**0.174**
	Splenium of corpus callosum	−0.001	0.000	p < 0.001	0.067
ODI	Cingulum – CC	0.001	0.000	0.003	0.024
	Cingulum – CH	0.001	0.000	0.002	0.026
	Genu of corpus callosum	0.001	0.000	p < 0.001	0.075
	Splenium of corpus callosum	0.001	0.000	p < 0.001	0.053
FISO	Cingulum – CC	0.000	0.000	0.977	0.000
	Cingulum – CH	0.004	0.001	p < 0.001	0.125
	Genu of corpus callosum	0.003	0.000	p < 0.001	0.103
	Splenium of corpus callosum	0.003	0.000	p < 0.001	0.091

Abbreviations: FA = fractional anisotropy; MD = mean diffusivity; NDI = neurite density index; ODI = orientation dispersion index; FISO = volume fraction of the isotropic diffusion compartment; Cingulum – CC = cingulum adjacent to the cingulate cortex; Cingulum – CH = cingulum bundle projections to the hippocampus.

with medium Cohen's effect sizes are provided in Supplementary **Fig. S1**.

DWI and cognition

The associations between the four parameters with medium Cohen's effect sizes and cognitive measures were next tested (Table 4). The analyses showed that higher NDI in the cingulum-CC was associated with higher Executive Function when controlling for age, sex, *APOE* ε4 genotype, and education. After controlling for multiple comparisons, no significant relationships were found for any of the other regions. However, since the association between MD in the cingulum-CC and Executive Function exhibited a medium Cohen's effect size, these variables were included in further analysis. Scatter plots of these associations are shown in Supplementary **Fig. S2**.

Sex, APOE ε4, AD parental history, and cardiovascular risk effects

After using the Bonferonni method for multiple comparisons, no significant associations were observed between the diffusion metrics and *APOE* ε4 carrier status, AD parental history, or cardiovascular risk. Sex showed significant associations only for MD and NDI in the cingulum-CH, but they did not meet the threshold for medium Cohen's effect size.

Age and cognition

There were significant negative associations between age and all three cognitive measurements: Immediate Learning ($\beta = -0.019 \pm 0.006$, $p = 0.001$), Delayed Recall ($\beta = -0.021 \pm 0.006$, $p < 0.001$), and Executive Function ($\beta = -0.046 \pm 0.005$, $p < 0.001$) in this sample of participants. Scatter plots of these associations are illustrated in Supplementary **Fig. S3**.

Age, DWI, and cognition

Based on the foregoing observations, a mediation analysis was performed to determine whether NDI in the cingulum-CC and MD in the cingulum-CC separately explain the relationship between age and Executive Function (Fig. 3). The mediation model confirmed the significant association between age and cingulum-CC NDI as well as the significant association between cingulum-CC NDI and Executive Function. The total effect of age on Executive Function was also confirmed to be significant; however, after taking into consideration the significant path via cingulum-CC NDI, the direct effect of age on Executive Function became attenuated (by 15%). These results are consistent with partial mediation, which suggests that while the association between age and Executive Function passes through white matter microstructure (cingulum-CC NDI), there are likely other mechanisms that contribute to that relationship (Fig. 3**a**). Similarly, the MD in the cingulum-CC was also shown to partially mediate the relationship between age and Executive Function. The direct effect of age on Executive Function became attenuated by 0.11% when taking into account MD in the cingulum-CC (Fig. 3**b**).

Discussion

In this study, we found that MD and NDI, compared to FA, ODI or FISO, were most influenced by aging. Out of the four regions of interest that were investigated, MD and NDI in the genu of corpus callosum and cingulum-CC appeared to be particularly vulnerable to aging. This difference in cingulum-CC NDI was also reflected in reductions in the cognitive measure of Executive Function. Overall, the results showed that age was associated with a decrease in Executive Function and that relationship was partially mediated by NDI and MD in cingulum-CC.

Microstructural differences in aging

The decline in NDI and MD with age is in good agreement with previous studies of aging populations [16,42]. When comparing NDI to other diffusion metrics, Merluzzi et al. [42] documented its superior sensitivity to aging in frontal white matter regions. That report also showed a link between neurite density and cognition, however the authors observed significant correlations with the RAVLT Total Learning score and the Trail Making Test, while in the present study, the significant associations were con-

Table 4
Associations between metrics with a medium Cohen's effect size and cognitive function.

Region of Interest	Composite Cognitive Score	B	Std. Error	Sig.	Cohen's Effect Size (f^2)
MD – Cingulum – CC	Immediate Learning	−0.654	2.120	0.758	0.000
	Delayed Recall	0.110	2.126	0.959	0.000
	Executive Function	*−4.201*	*1.892*	*0.027*	*0.015*
MD – Genu of corpus callosum	Immediate Learning	−1.983	1.041	0.058	0.011
	Delayed Recall	−1.348	1.047	0.199	0.005
	Executive Function	−1.306	0.938	0.165	0.006
NDI – Cingulum – CC	Immediate Learning	0.090	1.108	0.935	0.000
	Delayed Recall	−0.382	1.110	0.731	0.000
	Executive Function	**3.180**	**0.980**	**0.001**	**0.032**
NDI – Genu of corpus callosum	Immediate Learning	0.418	0.901	0.643	0.001
	Delayed Recall	0.378	0.904	0.676	0.001
	Executive Function	1.233	0.807	0.128	0.007

Abbreviations: MD = mean diffusivity; NDI = neurite density index; Cingulum – CC = cingulum adjacent to the cingulate cortex.

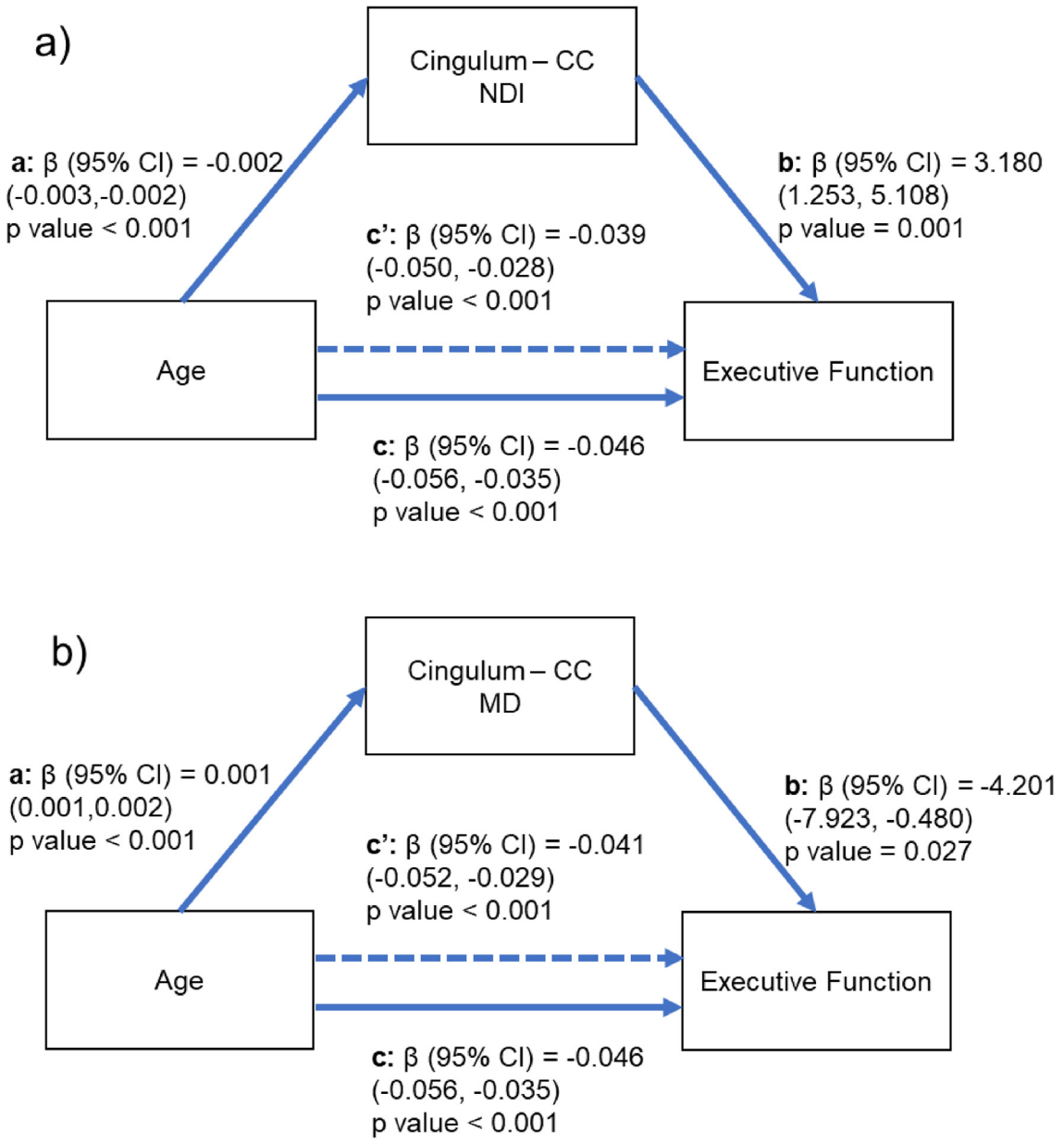

Fig. 3. The association between age and Executive Function is partially mediated by NDI in the cingulum-CC (a) and MD in the cingulum-CC (b). Graphic depiction of the mediation models: unstandardized parameter estimates are presented along with 95% confidence interval (CI) for each path of the mediation model. Note the c represents the total effect and c' the direct effect of age on Executive Function; NDI = neurite density index; Cingulum – CC = cingulum adjacent to the cingulate cortex, MD = mean diffusivity. The 95% CI for ab was estimated using the percentile bootstrapping method with 5000 bootstrapped samples.

fined to the Executive Function domain. A different study, focusing on white matter tracts, found MD to be the most sensitive to aging. They also showed that the observed changes in FA were largely driven by lower neurite density as opposed to greater dispersion [16]. While the two studies utilized different approaches, such as voxel-based analysis [42] and tract analysis [16], their region-specific results are consistent with those from our ROI analysis.

Other studies investigating the application of NODDI as a biomarker of aging, on the other hand, have observed findings not consistent with ours. A couple of them have reported no change in NDI [9] or an increase in NDI with age [11]. However, the majority of these studies examined much broader age ranges, including childhood and early adulthood, which limits the ability to make direct comparisons. Furthermore, there is evidence that diffusion trajec-

tories change non-linearly with age, emphasizing the importance of analyzing different age groups separately [11,16].

The regions of interest investigated in this report have been shown to be robustly affected by aging and AD. Previous studies have documented that areas in the medial temporal region, such as the hippocampus, have an increased vulnerability to aging. Kodiweera et al. [39] found that the left cingulum was particularly sensitive to aging, while the hippocampal segment of the cingulum had a moderate to low sensitivity [74]. The parahippocampal and posterior cingulate regions of the cingulum fibers have also shown DTI abnormalities in cognitively healthy older adults and those along the AD continuum [2,10,38,41]. Finally, measurements in these regions have also been shown to correlate with memory performance in MCI and AD patients [21,43] and non-demented older adults [1,9].

There are several potential mechanisms that can account for differences in diffusion as individuals age. In terms of pathological processes, NDI is a measure of intra-axonal water, so a direct loss of neurons would lead to an increase in the extra-neurite space, thus increasing MD and, in turn, decreasing NDI. One study investigating young onset AD has linked the decrease in NDI with loss of axons and overall density in a post-mortem histological analysis [60]. Myelin degeneration is another possible mechanism for reduced neurite density and increased mean diffusivity, which increases the extra-neurite space and indirectly leads to a reduction in the volume fraction of the intra-neurite space [58,68]. Conversely, the absence of significant ODI and FISO effects suggest that the age effect is not the primary driver of differences in neurite geometry or free water volume. On a more macroscopic scale, cerebrovascular health factors, such as perfusion [68] and fluid in the perivascular space [57,63] can influence diffusion and medial temporal regions are particularly susceptible to vascular damage [60]. While some histological studies have validated the NODDI metrics [15,27,55,70], more studies are necessary to fully characterize the differences in diffusion.

The link between healthy aging and neurocognitive performance has been documented numerous times [8,30,36,50,51,54], however, the mechanism by which this cognitive decline occurs has not been fully elucidated. In this report, we showed that the relationship is at least partially mediated by the decrease in neurite density and mean diffusivity, particularly in the cingulum-CC. In accord with our findings, several lines of evidence have documented associations between cingulum diffusion and Executive Function in healthy individuals [6,47]. One hypothesis suggests that the aging process leads to degradation of nerve fibers and loss of myelin which reduces transfer efficiency and in turn leads to cognitive decline [6,47]. Further investigation of the neurocognitive correlates of age-related white matter differences can be informative of the trajectories of cognitive decline.

Methodological considerations

The cohort used in this study is enriched with participants who have a family history of AD and consequently enriched for *APOE* ε4 genotype, which may limit the ability to generalize these results to the whole aging population. Furthermore, the sample population consisted of more women than men, which requires some consideration. Finally, a cross sectional study design may not be best suited to study the effects of aging. Longitudinal studies are needed to track individual trajectories over time.

Some consideration needs to be given to how diffusion data is collected and analyzed. *In vivo* diffusion metrics are indirect measures of diffusion and average signal from structures that are much smaller than the voxels. The biological properties, such as neurite density and orientation dispersion, are models applied to somewhat noisy data and are not direct measurements of these properties. Furthermore, it is important to consider the preprocessing steps that were taken prior to deriving the region of interest information and could impact the results, such as registration, interpolation, or partial volume effects. Finally, additional histological analyses are necessary to fully confirm the utility and accuracy of the NODDI technique.

Clinical impact/significance

While Diffusion Tensor Imaging is a sophisticated modeling technique that can capture complex fiber organizations, the biological processes that it represents are not very specific. NODDI, on the other hand, provides metrics that more precisely characterize the underlying cytoarchitecture of brain tissue and can provide additional information about aging trajectories. It is worth noting that the NODDI technique requires longer acquisition and processing time, compared to what is obtained with conventional DTI. However, both techniques may be particularly valuable in the preclinical phase of AD. This report showed complementary results that both MD and NDI are impacted by age-related differences in a healthy population at risk for AD. More specifically, MD had a stronger association with age, while NDI was more predictive of Executive Function. This suggests that DTI and NODDI metrics may provide complementary and clinically-relevant insights into white matter abnormalities. Finally, the NODDI technique can be implemented with standard diffusion sequences, thus making it accessible for routine clinical studies. By utilizing the DTI and NODDI techniques, this study demonstrated that there is an added clinical value to investing more scan time to collect advanced multi-shell datasets.

Conclusion

DTI and NODDI results were complementary, suggesting that white matter age-related differences are not strongly model-dependent. Age-related decline in NDI and increase in MD might partially represent the mechanisms leading to decline in Executive Function with age in a cohort of cognitively healthy older adults at risk for AD.

CRediT authorship contribution statement

Alice Motovylyak: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Nicholas M. Vogt:** Software, Validation, Data curation, Writing – review & editing. **Nagesh Adluru:** Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing. **Yue Ma:** Methodology, Formal analysis, Writing – review & editing, Visualization. **Rui Wang:** Conceptualization, Methodology, Writing – review & editing. **Jennifer M. Oh:** Software, Data curation, Writing – review & editing. **Steven R. Kecskemeti:** Software. **Andrew L. Alexander:** Software, Writing – review & editing, Funding acquisition. **Douglas C. Dean:** Software, Data curation. **Catherine L. Gallagher:** Writing – review & editing, Funding acquisition. **Mark A. Sager:** Writing – review & editing, Funding acquisition. **Bruce P. Hermann:** Writing – review & editing, Funding acquisition. **Howard A. Rowley:** Writing – review & editing, Funding acquisition. **Sterling C. Johnson:** Resources, Writing – review & editing, Funding acquisition. **Sanjay Asthana:** Resources, Writing – review & editing, Funding acquisition. **Barbara B. Bendlin:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition. **Ozioma C. Okonkwo:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Disclosure statement

The authors have no disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbas.2022.100030.

References

[1] Alm KH, Bakker A. Relationships between diffusion tensor imaging and cerebrospinal fluid metrics in early stages of the Alzheimer's disease continuum. J Alzheimer's Dis 2019;70(4):965–81. doi: https://doi.org/10.3233/JAD-181210.

[2] Alves GS, O'Dwyer L, Jurcoane A, Oertel-Knöchel V, Knöchel C, Prvulovic D, et al. Different patterns of white matter degeneration using multiple diffusion indices and volumetric data in mild cognitive impairment and Alzheimer patients. PLoS ONE 2012;7 (12):e52859. doi: https://doi.org/10.1371/journal.pone.0052859.

[3] Amlien IK, Fjell AM. Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. Neuroscience 2014;276:206–15. doi: https://doi.org/10.1016/j.neuroscience.2014.02.017.

[4] Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 2016;125:1063–78. doi: https://doi.org/10.1016/j.neuroimage.2015.10.019.

[5] Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 2011;54 (3):2033–44. doi: https://doi.org/10.1016/j.neuroimage.2010.09.025.

[6] Bartzokis G, Sultzer D, Lu PH, Nuechterlein KH, Mintz J, Cummings JL. Heterogeneous age-related breakdown of white matter structural integrity: Implications for cortical "disconnection" in aging and Alzheimer's disease. Neurobiol Aging 2004;25(7):843–51. doi: https://doi.org/10.1016/j.neurobiolaging.2003.09.005.

[7] Benedict RH. *Brief Visuospatial Memory Test – Revised*. Psychological Assessment Resources, Inc; 1997.

[8] Bettcher BM, Mungas D, Patel N, Elofson J, Dutt S, Wynn M, et al. Neuroanatomical substrates of executive functions: beyond prefrontal structures. Neuropsychologia 2016;85:100–9. doi: https://doi.org/10.1016/j.neuropsychologia.2016.03.001.

[9] Billiet T, Vandenbulcke M, Mädler B, Peeters R, Dhollander T, Zhang H, et al. Age-related microstructural differences quantified using myelin water imaging and advanced diffusion MRI. Neurobiol Aging 2015;36(6):2107–21. doi: https://doi.org/10.1016/j.neurobiolaging.2015.02.029.

[10] Catheline G, Periot O, Amirault M, Braun M, Dartigues J-F, Auriacombe S, et al. Distinctive alterations of the cingulum bundle during aging and Alzheimer's disease. Neurobiol Aging 2010;31 (9):1582–92. doi: https://doi.org/10.1016/j.neurobiolaging.2008.08.012.

[11] Chang YS, Owen JP, Pojman NJ, Thieu T, Bukshpun P, Wakahiro MLJ, et al. White matter changes of neurite density and fiber orientation dispersion during human brain maturation. PLoS ONE 2015;10(6): e0123656. doi: https://doi.org/10.1371/journal.pone.0123656.

[12] Chua TC, Wen W, Slavin MJ, Sachdev PS. Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review. Curr Opin Neurol 2008;21(1):83–92. doi: https://doi.org/10.1097/WCO.0b013e3282f4594b.

[13] Clark LR, Racine AM, Koscik RL, Okonkwo OC, Engelman CD, Carlsson CM, et al. Beta-amyloid and cognitive decline in late middle age: findings from the Wisconsin Registry for Alzheimer's Prevention study. Alzheimer's & Dementia: J Alzheimer's Assoc 2016;12 (7):805–14. doi: https://doi.org/10.1016/j.jalz.2015.12.009.

[14] Cohen J. Statistical power analysis for the behavior sciences. 2nd ed. Erlbaum; 1988.

[15] Colgan N, Siow B, O'Callaghan JM, Harrison IF, Wells JA, Holmes HE, et al. Application of neurite orientation dispersion and density imaging (NODDI) to a tau pathology model of Alzheimer's disease. NeuroImage 2016;125:739–44. doi: https://doi.org/10.1016/j.neuroimage.2015.10.043.

[16] Cox SR, Ritchie SJ, Tucker-Drob EM, Liewald DC, Hagenaars SP, Davies G, et al. Ageing and brain white matter structure in 3,513 UK Biobank participants. Nat Commun 2016;7(1). doi: https://doi.org/10.1038/ncomms13629.

[17] Daducci A, Canales-Rodríguez EJ, Zhang H, Dyrby TB, Alexander DC, Thiran JP. Accelerated microstructure imaging via convex optimization (AMICO) from diffusion MRI data. NeuroImage

2015;105:32–44. doi: https://doi.org/10.1016/j.neuroimage.2014.10.026.
[18] Dowling NM, Hermann B, la Rue A, Sager MA. Latent structure and factorial invariance of a neuropsychological test battery for the study of preclinical Alzheimer's disease. Neuropsychology 2010;24 (6):742–56. doi: https://doi.org/10.1037/a0020176.
[19] Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J. F., Duyckaerts, C., Epelbaum, S., Frisoni, G. B., Gauthier, S., Genthon, R., ... Jack, C. R. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. In *Alzheimer's and Dementia* (Vol. 12, Issue 3, pp. 292–323). Elsevier Inc. https://doi.org/10.1016/j.jalz.2016.02.002.
[20] Eaton-Rosen Z, Melbourne A, Orasanu E, Cardoso MJ, Modat M, Bainbridge A, et al. Longitudinal measurement of the developing grey matter in preterm subjects using multi-modal MRI. NeuroImage 2015;111:580–9. doi: https://doi.org/10.1016/j.neuroimage.2015.02.010.
[21] Ezzati A, Katz MJ, Lipton ML, Zimmerman ME, Lipton RB. Hippocampal volume and cingulum bundle fractional anisotropy are independently associated with verbal memory in older adults. Brain Imag Behavior 2016;10(3):652–9. doi: https://doi.org/10.1007/s11682-015-9452-y.
[22] Fortin J-P, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, et al. Harmonization of multi-site diffusion tensor imaging data. NeuroImage 2017;161:149–70. doi: https://doi.org/10.1016/j.neuroimage.2017.08.047.
[23] Fu X, Shrestha S, Sun M, Wu Q, Luo Y, Zhang X, et al. Microstructural white matter alterations in mild cognitive impairment and Alzheimer's disease study based on neurite orientation dispersion and density imaging (NODDI). Clin Neuroradiol 2020;30(3):569–79. doi: https://doi.org/10.1007/s00062-019-00805-0.
[24] Fukutomi H, Glasser MF, Zhang H, Autio JA, Coalson TS, Okada T, et al. Neurite imaging reveals microstructural variations in human cerebral cortical gray matter. NeuroImage 2018;182:488–99. doi: https://doi.org/10.1016/j.neuroimage.2018.02.017.
[25] Garyfallidis E, Brett M, Amirbekian B, Rokem A, van der Walt S, Descoteaux M, et al. Dipy, a library for the analysis of diffusion MRI data. Front Neuroinf 2014;8(FEB):1–17. doi: https://doi.org/10.3389/fninf.2014.00008.
[26] Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014 Jul 1;63(25 Pt B):2935-2959. doi: 10.1016/j.jacc.2013.11.005.
[27] Grussu F, Schneider T, Yates RL, Tachrount M, Tur C, Newcombe J, et al. Quantitative histological validation of NODDI MRI indices of neurite morphology in multiple sclerosis spinal cord. ISMRM 2015.
[28] Grussu F, Schneider T, Tur C, Yates RL, Tachrount M, Ianuş A, et al. Neurite dispersion: a new marker of multiple sclerosis spinal cord pathology? Ann Clin Transl Neurol 2017;4(9):663–79. doi: https://doi.org/10.1002/acn3.445.
[29] Guerreri M, Palombo M, Caporale A, Fasano F, Macaluso E, Bozzali M, et al. Age-related microstructural and physiological changes in normal brain measured by MRI γ-metrics derived from anomalous diffusion signal representation. NeuroImage 2019;188:654–67. doi: https://doi.org/10.1016/j.neuroimage.2018.12.044.
[30] Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. In *Clinics in Geriatric Medicine* (Vol. 29, Issue 4, pp. 737–752). https://doi.org/10.1016/j.cger.2013.07.002.
[31] Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis Second Edition A Regression-Based Approach*; 2017.
[32] Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimer's Dementia 2012;8(1):1–13. doi: https://doi.org/10.1016/j.jalz.2011.10.007.
[33] Jack CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dementia 2011;7(3):257–62. doi: https://doi.org/10.1016/j.jalz.2011.03.004.
[34] Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. NeuroImage 2012;62(2):782–90. doi: https://doi.org/10.1016/j.neuroimage.2011.09.015.
[35] Johnson, S. C., Koscik, R. L., Jonaitis, E. M., Clark, L. R., Mueller, K. D., Berman, S. E., Bendlin, B. B., Engelman, C. D., Okonkwo, O. C., Hogan, K. J., Asthana, S., Carlsson, C. M., Hermann, B. P., & Sager, M. A. (2018). The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions. In *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring* (Vol. 10, pp. 130–142). Elsevier Inc. https://doi.org/10.1016/j.dadm.2017.11.007.
[36] Kantarci K, Senjem ML, Avula R, Zhang B, Samikoglu AR, Weigand SD, et al. Diffusion tensor imaging and cognitive function in older adults with no dementia. Neurology 2011;77(1):26–34.
[37] Kellner E, Dhital B, Kiselev VG, Reisert M. Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn Reson Med 2016;76 (5):1574–81. doi: https://doi.org/10.1002/mrm.v76.510.1002/mrm.26054.
[38] Kiuchi K, Morikawa M, Taoka T, Nagashima T, Yamauchi T, Makinodan M, et al. Abnormalities of the uncinate fasciculus and posterior cingulate fasciculus in mild cognitive impairment and early Alzheimer's disease: a diffusion tensor tractography study. Brain Res 2009;1287:184–91. doi: https://doi.org/10.1016/j.brainres.2009.06.052.
[39] Kodiweera C, Alexander AL, Harezlak J, McAllister TW, Wu Y-C. Age effects and sex differences in human brain white matter of young to middle-aged adults: A DTI, NODDI, and q-space study. NeuroImage 2016;128:180–92. doi: https://doi.org/10.1016/j.neuroimage.2015.12.033.
[40] Koscik RL, La Rue A, Jonaitis EM, Okonkwo OC, Johnson SC, Bendlin BB, et al. Emergence of mild cognitive impairment in late middle-aged adults in the wisconsin registry for alzheimer's prevention. Dement Geriatr Cogn Disord 2014;38(1-2):16–30. doi: https://doi.org/10.1159/000355682.
[41] Lin Y-C, Shih Y-C, Tseng W-Y, Chu Y-H, Wu M-T, Chen T-F, et al. Cingulum correlates of cognitive functions in patients with mild cognitive impairment and early Alzheimer's disease: a diffusion spectrum imaging study. Brain Topogr 2014;27(3):393–402. doi: https://doi.org/10.1007/s10548-013-0346-2.
[42] Merluzzi AP, Dean DC, Adluru N, Suryawanshi GS, Okonkwo OC, Oh JM, et al. Age-dependent differences in brain tissue microstructure assessed with neurite orientation dispersion and density imaging. Neurobiol Aging 2016;43:79–88. doi: https://doi.org/10.1016/j.neurobiolaging.2016.03.026.
[43] Metzler-Baddeley C, Jones DK, Belaroussi B, Aggleton JP, O'Sullivan MJ. Frontotemporal connections in episodic memory and aging: a diffusion MRI tractography study. J Neurosci 2011;31 (37):13236–45. doi: https://doi.org/10.1523/JNEUROSCI.2317-11.2011.
[44] Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., Pose, C., Albala, B., Ropacki, M., Ritchie, C. W., & Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. In *Alzheimer's and Dementia* (Vol. 13, Issue 4, pp. 468–492). Elsevier Inc. https://doi.org/10.1016/j.jalz.2016.06.2365.
[45] Naggara O, Oppenheim C, Rieu D, Raoux N, Rodrigo S, Dalla Barba G, et al. Diffusion tensor imaging in early Alzheimer's disease. Psychiatry Res: Neuroimaging 2006;146(3):243–9. doi: https://doi.org/10.1016/j.pscychresns.2006.01.005.
[46] Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, et al. Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter. NeuroImage 2008;43(3):447–57. doi: https://doi.org/10.1016/j.neuroimage.2008.07.009.
[47] O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SCR, Markus HS. Evidence for cortical "disconnection" as a mechanism of age-related cogntive decline. Neurology 2001;57(4):632–8. doi: https://doi.org/10.1212/wnl.57.4.632.
[48] Parente DB, Gasparetto EL, Cruz LCHd, Domingues RC, Baptista AC, Carvalho ACP, et al. Potential role of diffusion tensor MRI in the differential diagnosis of mild cognitive impairment and Alzheimer's disease. Am J Roentgenol 2008;190(5):1369–74. doi: https://doi.org/10.2214/AJR.07.2617.
[49] Parker TD, Slattery CF, Zhang J, Nicholas JM, Paterson RW, Foulkes AJM, et al. Cortical microstructure in young onset Alzheimer's disease using neurite orientation dispersion and density imaging. Hum Brain Mapp 2018;39(7):3005–17. doi: https://doi.org/10.1002/hbm.24056.
[50] Peters BD, Ikuta T, DeRosse P, John M, Burdick KE, Gruner P, et al. Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. Biol Psychiatry 2014;75(3):248–56. doi: https://doi.org/10.1016/j.biopsych.2013.05.020.

[51] Reichman, W. E., Fiocco, A. J., & Rose, N. S. (2010). Exercising the brain to avoid cognitive decline: Examining the evidence. In *Aging Health* (Vol. 6, Issue 5, pp. 565–584). https://doi.org/10.2217/ahe.10.54.
[52] Reitan RM. The Halstead-Reitan neuropsychological test battery: Therapy and clinical interpretation. Neuropsychological Press; 1985.
[53] Sager MA, Hermann B, la Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. J Geriatr Psychiatry Neurol 2005;18(4):245–9. doi: https://doi.org/10.1177/0891988705281882.
[54] Salthouse T. Consequences of age-related cognitive declines. Annu Rev Psychol 2012;63(1):201–26. doi: https://doi.org/10.1146/annurev-psych-120710-100328.
[55] Sato, K., Kerever, A., Kamagata, K., Tsuruta, K., Irie, R., Tagawa, K., Okazawa, H., Arikawa-Hirasawa, E., Nitta, N., Aoki, I., & Aoki, S. (2017). Understanding microstructure of the brain by comparison of neurite orientation dispersion and density imaging (NODDI) with transparent mouse brain. *Acta Radiologica Open*, *6*(4), 205846011770381. https://doi.org/10.1177/2058460117703816.
[56] Schmidt M. Rey auditory verbal learning test: a handbook. Western Psychological Services; 1996.
[57] Sepehrband F, Cabeen RP, Choupan J, Barisano G, Law M, Toga AW. Perivascular space fluid contributes to diffusion tensor imaging changes in white matter. NeuroImage 2019;197:243–54. doi: https://doi.org/10.1016/j.neuroimage.2019.04.070.
[58] Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. NeuroImage 2016;131:81–90. doi: https://doi.org/10.1016/j.neuroimage.2015.09.071.
[59] Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2011;32(12):2322.e5–2322.e18. doi: https://doi.org/10.1016/j.neurobiolaging.2010.05.019.
[60] Slattery CF, Zhang J, Paterson RW, Foulkes AJM, Carton A, Macpherson K, et al. ApoE influences regional white-matter axonal density loss in Alzheimer's disease. Neurobiol Aging 2017;57:8–17. doi: https://doi.org/10.1016/j.neurobiolaging.2017.04.021.
[61] Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17(3):143–55. doi: https://doi.org/10.1002/hbm.10062.
[62] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's and Dementia 2011;7(3):280–92. doi: https://doi.org/10.1016/j.jalz.2011.03.003.
[63] Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Japanese J Radiol 2017;35(4):172–8. doi: https://doi.org/10.1007/s11604-017-0617-z.
[64] Teipel SJ, Wegrzyn M, Meindl T, Frisoni G, Bokde ALW, Fellgiebel A, et al. Anatomical MRI and DTI in the diagnosis of Alzheimer's Disease: A European multicenter study. J Alzheimer's Dis 2012;31(s3):S33–47. doi: https://doi.org/10.3233/JAD-2012-112118.
[65] Timmers I, Roebroeck A, Bastiani M, Jansma B, Rubio-Gozalbo E, Zhang H, et al. Assessing microstructural substrates of white matter abnormalities: a Comparative study using DTI and NODDI. PLoS ONE 2016;11(12):e0167884. doi: https://doi.org/10.1371/journal.pone.0167884.
[66] Tournier J-D, Smith R, Raffelt D, Tabbara R, Dhollander T, Pietsch M, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. NeuroImage 2019;202:116137. doi: https://doi.org/10.1016/j.neuroimage.2019.116137.
[67] Trenerry MR et al. The stroop neuropsychological screening test. Psychological Assessment Resources; 1989.
[68] Vemuri P, Lesnick TG, Przybelski SA, Graff-Radford J, Reid RI, Lowe VJ, et al. Development of a cerebrovascular magnetic resonance imaging biomarker for cognitive aging. Ann Neurol 2018;84(5):705–16. doi: https://doi.org/10.1002/ana.v84.510.1002/ana.25346.
[69] Veraart J, Novikov DS, Christiaens D, Ades-aron B, Sijbers J, Fieremans E. Denoising of diffusion MRI using random matrix theory. NeuroImage 2016;142:394–406. doi: https://doi.org/10.1016/j.neuroimage.2016.08.016.
[70] Wang N, Zhang J, Cofer G, Qi Y, Anderson RJ, White LE, et al. Neurite orientation dispersion and density imaging of mouse brain microstructure. Brain Struct Funct 2019;224(5):1797–813. doi: https://doi.org/10.1007/s00429-019-01877-x.
[71] Wechsler. (1981). *Wechsler Adult Intelligence Scale – Revised*. The Psychological Corporation, Harcourt brace & Co for The Psychological Corporation.
[72] Wechsler. Wechsler memory scale-revised. The Psychological Corporation, Harcourt Brace Jovanovich, Inc for Psychological Corp; 1987.
[73] Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage 2012;61(4):1000–16. doi: https://doi.org/10.1016/j.neuroimage.2012.03.072.
[74] Zhang Y, Schuff N, Jahng G-H, Bayne W, Mori S, Schad L, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. Neurology 2007;68(1):13–9. doi: https://doi.org/10.1212/01.wnl.0000250326.77323.01.