CHARACTERIZING WHITE MATTER MICROSTRUCTURE IN ASYMPTOMATIC OLDER ADULTS AT ELEVATED RISK FOR ALZHEIMER'S DISEASE

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Abstract

Growing evidence suggests that Alzheimer's disease (AD) is associated with axonal tract alterations. These white matter (WM) changes may emerge very early, prior to clinical symptom onset and may precede cortical grey matter changes. However, reliably characterizing these WM alterations *in vivo* and differentiating them from normal age-related change has been challenging. To address this challenge, the overarching goal of this dissertation was to examine differences in WM microstructure attributable to known AD-risk factors: age, genetics, and the presence of AD-related pathology. Advanced diffusion-imaging methods were used to characterize WM microstructure in a large sample of older adults at elevated familial risk for AD who remained clinically asymptomatic (n=146). Additionally, participants underwent genetic testing, lumbar punctures, and positron emission tomography (PET) scanning to derive AD-risk biomarkers. In Study 1, I implemented a multivariate, data-driven statistical technique, Partial Least Squares (PLS), to identify covariance patterns between whole-brain, voxelwise white matter microstructure and AD-risk factors. Neurite Orientation Dispersion and Density Imaging (NODDI) data were collected to derive three WM microstructure indices: neurite density (NDI), orientation dispersion (ODI), and isotropic volume fraction (ISOVF). Each of these measures was associated with age, APOE4 genotype, and amyloid-beta and tau pathology biomarkers. Older age was associated with all three NODDI WM indices. NDI was uniquely sensitive to AD-risk indexed by AD pathology biomarkers. Study 2 extended these analyses to examine WM microstructural associations with cognition (episodic memory, processing speed, and executive control) in the same preclinical AD cohort using a whole-brain exploratory approach. WM microstructure, indexed by NODDI, was associated with episodic memory and executive control. However, most associations did not remain when accounting for age-related variance, suggesting

that WM-cognition associations may not be specific to AD-risk factors. This dissertation represents one of the first, and among the most comprehensive investigations into WM microstructure in the context of multiple AD-risk factors, occurring before clinical syndrome onset. These findings demonstrate WM microstructural alterations are among the earliest neural changes to accompany AD-related pathology, providing a window into the impact of AD on brain structure, and informing novel opportunities for surveillance and intervention at the earliest disease stages.

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List of Abbreviations

Aβ – Beta-Amyloid
AD – Alzheimer's Disease
AD (Axial Diffusivity) – Axial Diffusivity
AMICO – Accelerated Microstructure Imaging via Convex Optimization
APOE – Apolipoprotein E
bPLS – Behavioral Partial Least Squares
BSR – Bootstrap Ratio
CI – Confidence Interval
CSF – Cerebrospinal Fluid
DKEFS – Delis-Kaplan Executive Function System
dMRI – Diffusion Magnetic Resonance Imaging
DTI – Diffusion Tensor Imaging
DW-MRI – Diffusion-Weighted Magnetic Resonance Imaging
DWI – Diffusion-Weighted Imaging
FA – Fractional Anisotropy
ISOVF – Isotropic Volume Fraction
LV – Latent Variable
MCI – Mild Cognitive Impairment
MCP-1 – Monocyte Chemoattractant Protein-1
MD – Mean Diffusivity
MMSE – Mini-Mental State Examination
MoCA – Montreal Cognitive Assessment
MPRAGE – Magnetization-Prepared Rapid Gradient Echo
MRI – Magnetic Resonance Imaging
NDI – Neurite Density Index
NODDI – Neurite Orientation Dispersion and Density Imaging
ODI – Orientation Dispersion Index
PART – Primary Age-Related Tauopathy
PET – Positron Emission Tomography
PLS – Partial Least Squares
PREVENT-AD – Preclinical Evaluation of Experimental or Novel Treatments for Alzheimer's Disease
p-tau – Phosphorylated Tau
RAVLT – Rey Auditory Verbal Learning Test
RD – Radial Diffusivity
SD – Standard Deviation
SUVR – Standardized Uptake Value Ratio
T2 FLAIR – T2 Fluid-Attenuated Inversion Recovery
TMT – Trail Making Test
t-tau – Total Tau
TREM2 – Triggering Receptor Expressed on Myeloid Cells 2

CHAPTER 1

General Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is marked by progressive neurocognitive impairments. Sporadic AD is the most prevalent form of the disease and typically develops after age 65, accounting for more than 95% of all cases (Harman, 2006). The primary risk factors for sporadic AD include advancing age, the presence of the apolipoprotein E ε4 allele (APOE4), and a parental family history (Kamiya et al., 2020). The development of AD is conceptualized through three stages of severity: preclinical AD is characterized by normal cognitive functioning with positive imaging or neurochemical biomarkers of AD; prodromal AD, as indicated by mild cognitive impairment (MCI); and AD dementia (Masters et al., 2015). The neuropathological course of AD spans 20–30 years, with brain changes beginning decades before the emergence of a clinical syndrome (Dubois et al., 2010; Sperling et al., 2011). This temporal disparity between the onset of neuropathological changes and overt clinical manifestations provides a window for early diagnosis and intervention, and highlights the importance of characterizing the earliest brain changes in AD. There is mounting evidence, summarized below, that brain changes at the preclinical, or asymptomatic, stage of the disease may manifest differently in cortex versus subcortical white matter. While the vast majority of studies examining brain changes in preclinical AD have focused on cortical or grey matter, in this dissertation I will examine the less-studied changes that occur in white matter as a function of the major risk factors and biomarkers of AD.

AD is associated with two core pathological processes: deposition of extracellular beta-amyloid (Aβ) plaques (Ikonomovic et al., 2008; Klunk et al., 2004; Nordberg, 2004) and neurofibrillary tangles arising from intracellular aggregation of hyper-phosphorylated tau

(Alonso et al., 1996). Extracellular Aβ plaque deposits develop in cortical regions (Serrano-Pozo et al., 2011) and have been associated with cortical atrophy (Oh et al., 2014). Neurofibrillary tangles aggregate in neuronal cell bodies and processes, leading to neural dysfunction and cell death (Knopman et al., 2021). Advances in biomarker research have allowed for the detection of *in vivo* changes or abnormalities indicative of underlying AD neuropathology that may precede the onset of the clinical syndrome. These biomarkers may be physiological, biochemical, or anatomical indicators that index pathological changes, aiding in diagnosis, prediction, or tracking of disease progression (Jack et al., 2010). Among these are positron emission tomography (PET) and cerebrospinal fluid (CSF) derived markers of Aβ plaque deposition and tau neurofibrillary tangles (Jack et al., 2018).

Early AD studies primarily focused on changes occurring in cortical and subcortical grey matter. More recently, post-mortem pathological studies and neuroimaging investigations have identified abnormalities in white matter as among the earliest indicators of AD-related neuropathology (Caso et al., 2016; Nasrabady et al., 2018). Evidence suggests these abnormalities in white matter may precede changes occurring in grey matter (Agosta et al., 2011; Amlien & Fjell, 2014; Canu et al., 2010; Maier-Hein et al., 2015; Parker et al., 2022; Salat et al., 2010; Stone et al., 2021; Stricker et al., 2013). Moreover, white matter changes have been associated with cognitive deficits that are the hallmark of the clinical syndrome (Bozzali et al., 2002; Huang et al., 2007; Scheltens et al., 1995; Takahashi et al., 2002; Zhuang et al., 2013), and these associations have been shown in both preclinical and early prodromal disease stages (Alm & Bakker, 2019). White matter alterations are also present in a range of diseases that co-occur with AD, including vascular and metabolic disorders (Santiago & Potashkin, 2021; Wassenaar et al., 2019). However, there is mounting evidence which suggests that these changes may also be

genetically related to the AD syndrome (Ferrer & Andrés-Benito, 2020). Taken together, these studies have demonstrated that white matter changes are a pathological feature of the AD syndrome. However, how these changes are associated with the major AD risk factors remains underspecified (Kamiya et al., 2020).

As noted above, advancing age, APOE genotype, and family history are the primary risk factors for sporadic AD (Kamiya et al., 2020). APOE is a glycoprotein involved in cholesterol transport, which is necessary for myelin maintenance and repair. Its efficacy depends on specific genetic variants, or alleles (Bartzokis, 2011; Mahley & Rall Jr, 2000). The APOE gene has three major alleles: epsilon-2, -3, and -4. APOE4 is the most significant genetic risk factor for AD (Ashford, 2004; Saunders et al., 1993) and is linked to the majority of sporadic AD cases before age 80 (Raber et al., 2004). It is associated with more rapid disease progression, marked by poor cholesterol regulation that results in disruption to myelin formation (Bartzokis, 2011; Blanchard et al., 2022). This provides a putative link between genetic AD risk and white matter integrity. Indeed, white matter degeneration has been observed in APOE4 carriers, even before the onset of clinical symptoms (Bagepally et al., 2012; Cai et al., 2017; Cavedo et al., 2017; Douaud et al., 2011; Dowell et al., 2013; Gold et al., 2010; Heise et al., 2014; Nierenberg et al., 2005; Persson, Lind, et al., 2006). Consistent with the idea of genetic determinants, family history is also a significant risk factor for AD. Individuals who have a family member with AD are 2–3 times more likely to develop AD dementia (Breitner et al., 1999; Huang et al., 2004) and this risk increases to 4–10 times for individuals with a first-degree relative (Cupples et al., 2004; Green et al., 2002; Silverman et al., 2005). In this dissertation, I will examine each of these risk factors—age, APOE4 genotype, and family history—as predictors of white matter microstructural integrity. However, before examining these associations, I will review several putative

mechanisms of white matter pathophysiology, and how they intersect with AD risk factors to promote a pathological cascade leading to white matter loss across the AD spectrum. While I do not examine these mechanisms of white matter pathophysiology directly in this dissertation, they provide the neurobiological links between the major AD risk factors examined here and the ultimate destruction of white matter over the disease course.

WHITE MATTER PATHOPHYSIOLOGY

Multiple mechanisms have been suggested to underlie white matter degeneration and demyelination in aging and AD. These include direct axonal damage or damage to oligodendrocytes, which are responsible for myelin formation and maintenance (Ferrer & Andrés-Benito, 2020; Nasrabady et al., 2018). These factors may interact, leading to reactive astrocytosis (Brun & Englund, 1986). Reactive astrocytosis occurs when the neuronal loss leads to abnormal increases in the number of surrounding astrocytes which become neurotoxic over the course of disease progression (Liddelow & Barres, 2017; Liddelow et al., 2017). While the specific mechanisms underlying both direct and indirect insults to the microstructural integrity of white matter remain an active area of inquiry (Caso et al., 2016; Liu et al., 2017), several putative factors have been proposed, and these are reviewed briefly in the next section.

Neuroinflammation

Neuroinflammation has been shown to play a critical role in the pathophysiology of white matter damage in AD. Immune system response, in the context of neuronal injury or infection, includes the activation of microglia and astrocytes, immune cells in the brain that release inflammatory signals including cytokines and chemokines. Although this is typically an adaptive response to injury, prolonged or excessive inflammatory responses have been shown to promote neurodegeneration (Kwon & Koh, 2020; see Adamu et al., 2024 for review). Age-related

changes to microglia and astrocyte function may exacerbate these effects (Bates et al., 2013; García-Matas et al., 2008; Salminen et al., 2011), leading to accelerated white matter changes in context of AD-related pathology (Liu et al., 2017). While Aβ plaques are not commonly found in white matter, elevated soluble Aβ concentrations have been reported (Collins-Praino et al., 2014) and these are toxic to oligodendrocytes (Desai et al., 2011; Desai et al., 2010; Jantaratnotai et al., 2003; Lee et al., 2004; Xu et al., 2001; see Nasrabady et al., 2018 for review). Over the disease course the efficacy of immune cells in clearing Aβ aggregates declines, promoting neuroinflammatory responses. Persistent activation of microglia further increases Aβ accumulation, resulting in neurotoxicity and accelerating the inflammatory cascade (McQuade & Blurton-Jones, 2019). In addition, genetic mutations in TREM2 and CD33, implicated in astroglial reactivity, can increase AD-related neurodegeneration by altering microglial function, hindering the clearance of debris associated with myelin breakdown, ultimately leading to axonal injury (Griciuc et al., 2019; Winfree et al., 2022) and an accelerating cycle of axonal pathology (Clarner et al., 2012).

Chronic inflammation also impairs the ability of oligodendrocytes to regenerate myelin, a process crucial for maintaining white matter integrity over the life course (Akassoglou et al., 1998; Graf et al., 2014; Santos et al., 2018). Additionally, the inflammatory molecule S100B interferes with oligodendrocyte differentiation, maturation, and function, compounding white matter dysfunction (Santos et al., 2018). In preclinical AD, neuroinflammatory markers, such as monocyte chemoattractant protein-1 (MCP-1), have also been associated with tau pathology and axonal degeneration (Melah et al., 2016), providing a further link between inflammatory processes and white matter health. Moreover, inflammation and oxidative stress from reactive astrocytosis have been linked to myelin dysfunction and increased Aβ deposition (Depp et al.,

2023) which, in turn, contribute to myelin damage (Misonou et al., 2000; Tejera et al., 2019), and an accelerating cycle of pathology.

Microvascular Changes

The etiology of AD-related white matter damage has also been associated with alterations to local microvasculature (Brun & Englund, 1986; Sjobeck et al., 2006) leading to pathological vascular Aβ accumulation (Haglund & Englund, 2002; Tian et al., 2004). The brain's microvasculature is made up of microscopic arterioles that deliver blood, oxygen, and nutrients directly to tissue. White matter is particularly vulnerable to microvascular dysfunction (Agarwal & Carare, 2021), elevating the risk of white matter hypoperfusion in older adulthood which may be further in increased AD (Liu et al., 2017). Further, these age-related vascular changes can lead to compromised perivascular drainage throughout the brain, leading to reduced clearance of Aβ (Brown & Thore, 2011). Increased Aβ deposition has been shown to compromise blood flow, leading to further microvascular dysfunction (Roher et al., 1993) and disrupting the formation of new blood vessels (Yang et al., 2023). In addition, loss of cholinergic tone, another prominent feature of AD-related pathology, leads to disruptions in blood flow regulation which, combined with Aβ deposition and reduced Aβ clearance, can exacerbate hypoperfusion leading to accelerated white matter damage in AD (Liu et al., 2017). Indeed, recent evidence suggests that these vascular changes may be a necessary factor for the development of clinical symptoms in individuals who have underlying AD-related pathology (Bagi et al., 2023).

Wallerian Degeneration

The Wallerian degeneration hypothesis of white matter loss in aging and brain disease proposes that degeneration of white matter fibre tracts occurs secondary to cortical degeneration

(Coleman, 2005). However, recent *ex vivo* and *in vivo* studies (reviewed below) have shown that white matter damage can occur independently of grey matter atrophy, and microstructural abnormalities in white matter can be detected at the earliest stages of AD, before cortical changes manifest (Brun & Englund, 1986; Englund & Brun, 1990; Sachdev et al., 2013; see Caso et al., 2016 for review). While Wallerian degeneration likely contributes to white matter atrophy in later disease stages, increasing evidence suggests that white matter degeneration may be a precursor of cortical changes at the very earliest stages of disease (Agosta et al., 2011; Amlien & Fjell, 2014; Canu et al., 2010; Maier-Hein et al., 2015; Parker et al., 2022; Salat et al., 2010; Stone et al., 2021; Stricker et al., 2013), highlighting the importance of mapping white matter changes across all stages of AD.

A key empirical challenge in this regard has been to detect microstructural white matter changes *in vivo*. In the next sections I review the neuroimaging techniques most commonly used to examine white matter microstructure in aging and brain disease.

IN-VIVO MEASUREMENT OF WHITE MATTER INTEGRITY

In vivo white matter microstructural changes have been primarily studied using diffusion-weighted imaging (DW-MRI) (Le Bihan et al., 1986). Structural MRI scans such as T2 Fluid Attenuated Inversion Recovery (T2 FLAIR) provide macrostructural measures of white matter, including volume and shape. DW-MRI quantifies white matter microstructural properties such as myelination, axonal diameter, density, and membrane permeability. This is accomplished by measuring the diffusion motion of water molecules to distinguish between different tissue types. In white matter tracts, water molecules are directed and constrained by myelin, leading to an anisotropic pattern of diffusion that provides a unique MR signature from that obtained in cerebral spinal fluid and grey matter, where diffusion is more isotropic (Le Bihan et al., 2001;

Pierpaoli & Basser, 1996; Pierpaoli et al., 1996). Below, I first review the most commonly reported approach for measuring white matter structural integrity, diffusion tensor imaging (DTI). Next, I will review a new approach to modelling DWI signal that provides a more precise estimate of white matter microstructural integrity: Neurite Orientation Direction and Dispersion Imaging (NODDI), which is the focus of this dissertation.

Diffusion Tensor Imaging

The most commonly reported DW-MRI measures are derived from a tensor-based diffusion model. Diffusion tensor imaging (DTI) characterizes white matter integrity using three primary metrics. Fractional anisotropy (FA) indexes the magnitude of the primary diffusion direction (Pierpaoli & Basser, 1996), which is determined by fibre density, axonal diameter, and myelination (Yin et al., 2015). Higher FA values are considered to represent more intact fibre pathways. Mean diffusivity (MD) is a summary measure of molecular diffusion rate, or average diffusion across three orthogonal directions (Caso et al., 2016). Lower MD values typically indicate restricted diffusion, which can be associated with intact tissue structure, higher cell density, or more organized cellular membranes. Higher MD values indicate more isotropic diffusion, indicative of tissue damage, decreased cell density, or disruption of cellular membranes (Soares et al., 2013). MD can be further subdivided into radial (RD) and axial (AD) diffusivity. RD refers to diffusion along the tensor's longitudinal axis, whereas RD captures diffusion along the perpendicular axis.

Increased MD and decreased FA are commonly reported as indicators of white matter damage. In AD, damage to cell membranes leads to more isotropic diffusion of water molecules, resulting in higher MD and lower FA (Agosta et al., 2011; Bergamino et al., 2021; Falgàs et al., 2019; Jack, 2012; Stone et al., 2021; Vaquer-Alicea & Diamond, 2019; Yu et al., 2017; Zhang et

al., 2007). While DTI has been the gold-standard for characterizing microstructural changes in white matter *in vivo*, this technique has several limitations.

DTI uses a signal representation approach to extract information from diffusion MRI data. A signal representation approach enhances *sensitivity* to target pathologies but lacks a clear biological interpretation due to a lack of *specificity* for individual tissue microstructure features (Pierpaoli et al., 1996). For example, variability in FA values can represent a range of underlying microstructural changes in tissue such as altered axonal packing density or axonal orientation dispersion (i.e., how scattered or spread-out axons are within a target region) (Beaulieu, 2014). DTI metrics are also influenced by a variety of structural or physiological features including crossing fibre pathways, permeability of the axonal membrane, inflammation, or edema (Araque Caballero et al., 2018; Jones et al., 2013; Song et al., 2018). Further, age-related partial volume effects may bias voxel-wise estimates of fibre integrity as increased CSF, particularly around ventricular regions, can artifactually lower FA values (Concha, 2014). Finally, the sensitivity of DTI to detect individual or group differences in white matter integrity may vary depending on the specific fibre track (Araque Caballero et al., 2018). However, recent advances in DWI imaging acquisition and signal modeling protocols are addressing these challenges, providing more precise estimates of white matter microstructural integrity in aging and brain disease.

Neurite Orientation Dispersion and Density Imaging (NODDI)

Neurite Orientation Dispersion and Density Imaging (NODDI) is a diffusion-weighted imaging technique that characterizes neurite morphology based on a biophysical model of tissue cytoarchitecture (Timmers et al., 2016; Zhang et al., 2012). NODDI modeling segregates the diffusion MRI signal into three components: intraneurite, extraneurite, and free water. When applied to white matter, the intraneurite compartment models the intrastructural integrity of

axons, characterized by highly restricted diffusion in the space bounded by the neurite (i.e., axonal) membrane. The extraneurite compartment models microglia, astrocytes, oligodendrocytes, neuronal cell bodies, ependymal cells, extra-cellular matrices, and vascular structures that hinder diffusion outside of neurites. The free water compartment models space occupied by CSF, which is characterized by isotropic (i.e., free) diffusion (Zhang et al., 2012). Estimating the volume fraction of CSF allows for NODDI to address the effects of CSF contamination (Zhang et al., 2012), which is particularly prominent in periventricular white matter structures (e.g., corpus callosum and the fornix) (Metzler-Baddeley et al., 2012), and is exacerbated in AD (Mielke et al., 2009; Nowrangi et al., 2013; Teipel et al., 2016).

Three NODDI indices are derived from the DWI signal to index these tissue compartments. The **neurite density index (NDI)** is a proxy for axonal packing density within a voxel and represents the fraction of tissue that comprises axons, also referred to as intra-neurite volume fraction. In healthy white matter, NDI is expected to be higher and to be reduced in regions with axonal thinning and degeneration (Colgan et al., 2016; Grussu et al., 2017).

The **orientation dispersion index (ODI)** represents dispersion (i.e., angular variation and spatial configuration) in axonal organization. In white matter, regions with high ODI values are believed to indicate highly dispersed axons, while lower values are associated with well-aligned and tightly organized structures such as white matter tracts (Eaton-Rosen et al., 2015; Zhang et al., 2012). However, unlike with the other NODDI metrics, there is no clear biophysical mechanism to link alterations in ODI to an underlying pathological process (e.g., demyelination, inflammation, or atrophy) (Raghavan et al., 2021). In addition, axonal loss can lead to either an increase or decrease in ODI depending on the original alignment of the fibres. For example, if axons run parallel to a fibre bundle, losing those axons would lead to an increase in ODI because

there would be less alignment among the remaining fibres. By contrast, if axons run perpendicular to another fibre bundle (i.e., crossing fibres) losing those axons would lead to a decrease in ODI because there would be fewer spreading fibres (Raghavan et al., 2021).

The **isotropic volume fraction (ISOVF)** represents freely diffusing water in the extracellular space, which is high in CSF and low in tissue (i.e., white matter). Isotropic diffusion is a type of unhindered diffusion where particles move evenly in all directions (i.e., isotropically). In the context of neuronal atrophy or death, the structure of neurites (axonal projections, in the case of white matter) becomes compromised. When neurites lose their structural integrity, they no longer act as barriers to extracellular water movement. As a result, CSF can diffuse more freely, leading to an increase in the measurement of free water (Gullett et al., 2020; Maier-Hein et al., 2015; Ofori et al., 2015; Pasternak et al., 2009). In contrast to MD in DTI, which is a general measure of diffusion across all directions that reflects both unrestricted and restricted diffusion, ISOVF provides a more precise measure of *unrestricted* diffusion. As such, ISOVF indexes white matter areas where CSF diffusion is not directionally constrained. While MD can be influenced by various factors, including changes in both intra-axonal and extracellular environments, ISOVF exclusively represents the proportion of water that is not constrained by cellular or tissue structure in the *extracellular* environment (Colgan et al., 2016).

NODDI Model Advantages

NODDI leverages multi-shell diffusion MRI (dMRI) to derive these indices of white matter integrity (Kamiya et al., 2020). Multi-shell acquisitions have been shown to be more reliable than single shell acquisitions (Bergamino et al., 2021; Golub et al., 2021). Multi-shell dMRI uses sets of diffusion-weighted images acquired with different diffusion sensitivities (i.e., multiple gradient shells) which enables modelling of complex diffusion patterns. As

demonstrated in the original work by Zhang et al. (2012), NODDI is particularly effective at mapping white matter microstructures due to its increased *specificity*. It can distinguish between axonal packing density and orientation dispersion, which are indistinguishable in FA measures (see above). In addition, DWI studies have demonstrated that accounting for free water (which NODDI accomplishes with the ISOVF metric) provides more specific measures of white matter integrity in older adults (Chad et al., 2018).

In addition to increased specificity, NODDI appears to be more *sensitive* than DTI. NODDI can account for partial volume effects of CSF that result in DTI imaging artifacts (Parker et al., 2018; Raghavan et al., 2021). It distinguishes between different tissue compartments more accurately and explicitly models neurites (axons and dendrites), extracellular space, and isotropic compartments (such as CSF) separately. This allows NODDI to better account for partial volume effects arising from the mixing of different tissue types within a voxel. As noted earlier, ODI and NDI are thought to capture distinct features represented by the single FA metric in DTI (Zhang et al., 2012). Critically, NODDI metrics are more strongly associated with post-mortem histological data (Grussu et al., 2017; Schilling et al., 2018; Sepehrband et al., 2015), suggesting these measures provide more biologically plausible *in vivo* measures of white matter integrity than the DTI metrics. Similar to DTI, NODDI shows excellent scan-rescan reliability, with the variation in specific measurements (NDI and ODI) typically being less than 5% between repeat scans (Andica et al., 2020; Chang et al., 2015; Chung et al., 2016; Granberg et al., 2017; Huber et al., 2019; Tariq et al., 2012).

The enhanced *sensitivity* and *specificity* offered by NODDI can support more accurate diffusion-weighted estimates of white matter microstructural alterations resulting from pathophysiological processes related to AD such as demyelination, axonal damage, neuronal

loss, and inflammation (Aye et al., 2022; Ehrenberg et al., 2018; Weiskopf et al., 2013). In addition, NODDI's acquisition protocol is time efficient, allowing it to be gathered easily in clinical settings (Zhang et al., 2012).

Both conventional methods and emerging models in DWI-MRI have offered avenues to measure white matter pathophysiology at the microstructural level *in vivo*. Given the relative novelty of the NODDI approach, there are few published studies in aging and AD as compared to studies reporting DTI findings. As such, in the next section I will review the findings of both approaches to inform my hypotheses regarding associations between AD-risk factors and white matter structural integrity. I will briefly review evidence for age-related changes as a baseline for changes observed across the AD-spectrum.

WHITE MATTER MICROSTRUCTURAL INTEGRITY IN AGING AND AD

DTI in Typical Aging

DTI studies have demonstrated that as individuals age, the integrity of white matter in the brain declines (Bennett & Madden, 2014), a process that begins between ages 30-50 (Kochunov et al., 2012; Lebel et al., 2012; Sexton et al., 2014) and is believed to accelerate with age (Sexton et al., 2014). This decline in white matter integrity outpaces the loss of grey matter over time (Guttmann et al., 1998). With increasing age, a general decrease in FA and an increase in MD values has been observed across both cross-sectional and longitudinal DTI studies (Wassenaar et al., 2019). Radial diffusivity also increases with advancing age, suggestive of decreased myelin integrity (Madden et al., 2012). When co-occurring, axial and radial diffusion increases are thought to be an indicator of age-related damage to the axons themselves as well as to the surrounding myelin (Madden et al., 2012), a marker of more severe damage.

DTI in Atypical Aging

Preclinical AD marks the transition from typical aging to atypical, or pathological aging, on a neurobiological level. Preclinical AD can be tracked by examining cognitively unimpaired individuals who have the AD risk factors previously mentioned (i.e., increased age, presence of apolipoprotein E ε4 allele, and parental family history) (Kamiya et al., 2020) as well as biomarker evidence suggestive of underlying disease pathology (e.g., CSF and PET markers of AD pathology burden). This approach assists with early detection and disease staging.

In their review, Alm and Bakker (2019) summarized findings from studies examining at-risk individuals based on familial predisposition or APOE4 carrier status. They observed that white matter microstructure was characterized by abnormalities (defined as decreased FA and/or increased MD) in the parahippocampus (Honea et al., 2009; Nierenberg et al., 2005; Smith et al., 2010), cingulum, uncinate fasciculus, and corpus callosum (Bendlin et al., 2010; Gold et al., 2010; Heise et al., 2011; Persson, Lind, et al., 2006; Smith et al., 2010; see Gold et al., 2012 for review). With respect to longitudinal changes, the corpus callosum (Teipel et al., 2016) and fornix (Mielke et al., 2009; Nowrangi et al., 2013) have been shown the greatest vulnerability in an at-risk, preclinical sample. It has also been suggested that AD-related microstructural white matter changes follow a progression pattern starting in the limbic tracts, followed by lateral temporoparietal association tracts, commissural fibres of the splenium, and lastly affecting the long-range association pathways involving frontal white matter. The microstructural changes in the limbic tract include the fornix, uncinate fasciculus, and posterior and parahippocampal fibres of the cingulum. They are the most pronounced and appear years prior to grey matter or cognitive changes (Teipel et al., 2016). Collectively, these findings illustrate a relationship between the earliest stages of AD progression and microstructural changes in white matter.

In conjunction with familial and genetic risk factors, abnormal measures of Aβ42 and phosphorylated tau (biomarkers of AD pathology burden) are associated with widespread alterations in white matter microstructure throughout the brain in preclinical samples. These are typically measured from CSF, extracted via lumbar puncture, or through PET imaging using amyloid or tau binding radioligand tracers. In cognitively normal older adults with lower levels of circulating Aβ42 in CSF (an index of higher amyloid plaque deposition), reductions in FA have been noted most often in the fornix, cingulum, parahippocampal cortex, and inferior temporal gyrus (see Alm & Bakker, 2019 for review). Persons with high neurofibrillary tangle aggregation —indexed by higher CSF phosphorylated (p-tau) or total tau (t-tau)—also exhibit reductions in FA, but more commonly demonstrate a pattern of significantly elevated MD in the fornix, precuneus, ventral cingulum tracts, and entorhinal white matter (Kantarci et al., 2017; Stenset et al., 2011). These two diffusion abnormality patterns (reduction in FA and increase in MD) have been associated with the clinical trajectory and may predict progression to MCI (Ten Kate et al., 2018).

Recent work suggests that considering markers of AD pathological burden in isolation may be a less sensitive approach for predicting the risk of clinical disease. As such, ratio markers have been derived, including p-tau/Aβ42 and t-tau/Aβ42 (Bendlin et al., 2012; Gold et al., 2014; Hoy et al., 2017; Racine et al., 2019). In cognitively normal individuals, abnormal ratios (indicating elevated p-tau or t-tau and low Aβ42) have been associated with decreased FA and increased diffusivity (MD, AD, RD) across multiple brain regions (Alm & Bakker, 2019).

A non-linear association between Aβ-PET and white matter tract microstructure has also been described (Dong et al., 2020; Wolf et al., 2015). In cognitively unimpaired older adults, an initial increase in Aβ levels has been associated with higher FA and lower diffusivity measures.

As Aβ levels continue to rise, FA reaches its peak, and diffusivity measures hit their lowest point. With further increases in Aβ levels, FA decreases, and diffusivity measures increase (Collij et al., 2021; see Alm & Bakker 2019 for review). This suggests that in preclinical AD, white matter may first exhibit compensatory changes in response to early Aβ pathology, followed by subsequent axonal degeneration with continued Aβ accumulation.

NODDI in Typical Aging

Changes in neurite morphology such as orientation dispersion and neurite density serve as critical indicators of both brain development and aging (Conel, 1939; Jacobs et al., 1997). NODDI has become quickly favoured for its capacity to offer precise and reliable insights into the impact of aging on brain white matter microstructure (Beck et al., 2021; Billiet et al., 2015; Chang et al., 2015; Kodiweera et al., 2016; Merluzzi et al., 2016; Qian et al., 2020). Studies comparing multiple DWI metrics have consistently identified NODDI to be more sensitive to age-related white matter changes than other metrics, including DTI (see Beck et al., 2021; Guerreri et al., 2019; Ota et al., 2017).

While the general finding has been that NDI rapidly decreases with age (Merluzzi et al., 2016; Raghavan et al., 2021), inconsistencies have been observed. Preliminary studies applying NODDI in an aging context reported that NDI continues to increase with age until *middle-late* adulthood (~60-70s) (Chang et al., 2015), though increases in adulthood are slower (Billiet et al., 2015). However, these studies were limited by restricted cohort sampling, with few participants over 70. The studies that followed suggested a more complex relationship between NDI and age that exhibits a quadratic, inverted U-shape association. In sampling more broadly into older adulthood (i.e., ~80-90s), it was observed that NDI increases up until age 40 before declining, with more rapid decreases observed in the sixth and seventh decades of life. This suggests

widespread loss of axonal packing density beginning in middle age (Beck et al., 2021; Cox et al., 2016; Gozdas et al., 2021; Qian et al., 2020). This pattern has been shown to parallel patterns of demyelination, indexed by the myelin water fraction (Qian et al., 2020). Interestingly, reduced NDI in specific white matter tracts predict NDI values in their cortical endpoints and these changes have been associated with cognitive performance (Gozdas et al., 2021). In a sample of 55-81-year-olds, the impact of age on NDI was most robustly observed in association tracts (i.e., cingulum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus). These results suggested that brain regions with higher axonal packing density and greater metabolic activity might be particularly vulnerable to age-related change (Raghavan et al., 2021).

ODI also shows sensitivity to white matter microstructural changes in aging (Beck et al., 2021; Guerreri et al., 2019). In a large study (n=3,513), ODI was reported to show a nonlinear increase until *early* older adulthood (~60 years) followed by a decrease (Cox et al., 2016). However, more recent studies including longitudinal investigations, suggest that ODI exhibits a steady increase (Billiet et al., 2015; Chang et al., 2015; Guerreri et al., 2019) until *late* older adulthood (~80 years) at which point the slope stabilizes (Beck et al., 2021). However, these cross-study differences are likely attributable to variability in the constitution and size of the age cohorts (Beck et al., 2021; Cox et al., 2016; Guerreri et al., 2019). Age-related alterations in ODI also shows regional specificity, depending on tract tortuosity and the presence of crossing fibres (Raghavan et al., 2021). ODI has been shown to remain generally stable into *later* older adulthood with the exception of the right and left corticospinal tracts (Gozdas et al., 2021). However, in separate investigations, the corpus callosum exhibited lower ODI attributed to reduced tract complexity, in contrast to higher ODI in regions including the fornix, cingulum, and parahippocampal cingulum, attributable to increased loosening, fanning and potential

bending of axonal bundles with age (Cox et al., 2016; Guerreri et al., 2019; Kodiweera et al., 2016). These findings are thought to be evidence of ongoing remodelling of white matter over the lifespan that becomes more notable after age 60 (Raghavan et al., 2021).

Though less frequently investigated, ISOVF has been consistently found to increase with aging (Beck et al., 2021; Billiet et al., 2015; Guerreri et al., 2019; Merluzzi et al., 2016; Raghavan et al., 2021). These findings align with histological evidence demonstrating that with older age, the concentration of interstitial free water in the extracellular space is higher in certain brain regions (Chad et al., 2018; Meier-Ruge et al., 1992). Though the specific mechanisms underlying these increases in extracellular free water are unknown, age-related cerebrovascular neural degenerative processes have been associated with cell shrinkage (Merluzzi et al., 2016), edema (Pasternak et al., 2009), and neuroinflammatory responses (Wang et al., 2011).

NODDI in Atypical Aging

Though in its infancy, investigations of NODDI in white matter suggest that these measures are more sensitive than DTI metrics to white matter integrity changes across the AD spectrum (Fu et al., 2020; Moody et al., 2022; Slattery et al., 2017). This is in part due to NODDI's ability to disentangle fractional anisotropy (from DTI) into indices of neurite density (NDI) and orientation dispersion (ODI) (Fu et al., 2020; Slattery et al., 2017). In AD, the vast majority of DTI studies have observed reduced FA. However, these estimates can be confounded by crossing fibres and complex axonal dispersion patterns related to selective sparing or degeneration of specific fibre tracts which result in spurious FA measures (Douaud et al., 2011). Given this field of inquiry is in its early stages, with few studies focusing on preclinical populations (the focus of this dissertation), the following review takes a broad focus on characterizing current findings across the AD spectrum.

NDI has been shown to be a more sensitive marker of AD-related changes in white matter than FA (Fu et al., 2020; Slattery et al., 2017). Broadly, NDI declines across the AD spectrum, with more severe stages of AD associated with greater reductions in NDI (Fu et al., 2020; Gozdas et al., 2021; Slattery et al., 2017; Wen et al., 2021). Among NODDI and DTI metrics, NDI demonstrated the greatest sensitivity to clinical staging (cognitively unimpaired vs. MCI vs. dementia), with reductions in NDI correlating with increased disease severity. While DTI metrics were sensitive to differences between MCI and AD, they did not differentiate between cognitively unimpaired controls and MCI at earlier stages of the disease. In contrast, NDI was able to reliably distinguish between these early-stage disease cohorts (Fu et al., 2020). In cognitively unimpaired individuals with familial AD-risk, NDI is sensitive to age-related changes, particularly in the genu of the corpus callosum and cingulum-corpus callosum bundles (Motovylyak et al., 2022). At the time of writing, there were no studies that applied NODDI to examine white matter microstructural associations with APOE4 carrier status in sporadic AD. However, in young-onset AD, NDI has been shown to decrease compared to cognitively unimpaired controls (Veale et al., 2021), with more widespread decreases noted in APOE4 carriers compared to non-carriers (Slattery et al., 2017).

ODI has been observed to exhibit both increases and decreases in AD. In a study comparing individuals across the broad disease spectrum (cognitively unimpaired, MCI, dementia), reductions in ODI were associated with increased disease severity (Fu et al., 2020). Compared to cognitively unimpaired controls, MCI participants exhibited ODI reductions in the cingulum, bilateral superior longitudinal fasciculus, and bilateral corticospinal tract. AD participants also exhibited reductions in the bilateral superior longitudinal fasciculus and left cingulum when compared to MCI, but not the corticospinal tract. However, in studies only

examining cognitively unimpaired controls and patients with MCI, ODI increases differentiated MCI from control groups (Gozdas et al., 2021; Wen et al., 2019). For example, Gozdas et al. (2021) reported higher ODI in the cingulum-cingulate bilaterally and cingulum hippocampus, and lower ODI in the corticospinal tracts bilaterally in MCI versus cognitively unimpaired controls. Similarly, Wen et al. (2021) reported higher ODI in the cingulum, thalamic radiations, and forceps major in MCI. In cognitively unimpaired individuals with familial AD-risk, variations in ODI do not appear to be influenced by age in the same way as variations in NDI (Motovylyak et al., 2022). These conflicting results suggest that myriad factors, including both typical aging and pathological processes may underly changes in axonal organization, as indexed by ODI, in the earliest, preclinical disease stages.

Compared to the other NODDI metrics, ISOVF has only been examined across two studies in AD. ISOVF increases have been associated with increased disease severity across the clinical AD continuum (Fu et al., 2020). However, differences in ISOVF were not observed in preclinical populations (Motovylyak et al., 2022).

As noted in the introduction, risk of conversion from preclinical stages to the prodromal or clinical AD syndrome is associated with age, genetics, and family history. However, *in-vivo* biomarkers have also been developed to index AD risk in asymptomatic older adults. These include CSF-derived markers of circulating pathology and PET-derived measures of pathological burden. In the next section I review evidence of associations between these biomarkers and NODDI measures of white matter structural integrity.

NODDI AND AD BIOMARKER ASSOCIATIONS

In non-human animal (mouse) models of AD, white matter NDI is reduced in the presence of tau pathology but increased in AD-type Aβ deposition models (Colon-Perez et al.,

2019). In human studies, weak negative associations have been observed between Aβ-PET and NDI across the AD spectrum. Specifically, higher levels of Aβ burden have been related to NDI reductions in the parahippocampal cingulum (Raghavan et al., 2021). While this study did not identify NDI-related associations with tau-PET, another study reported that tau-related white matter degeneration was also associated with decreased NDI (Wen et al., 2021). This may be related to hyperphosphorylation of tau decreasing microtubule binding and intra-axonal cytoskeleton deterioration (Alonso et al., 1996) or Wallerian degeneration of axons and demyelination due to increased cortical tau pathology (McAleese et al., 2017). In a sample of Aβ+ participants, negative relationships between NDI and tau deposition were observed in the uncinate fasciculus and the cingulum, both fibre pathways structurally linked to regions of initial tau deposition (Tian et al., 2023). Along with earlier studies, these results suggest that NDI values spatially correlate with patterns of tau protein deposition (Fu et al., 2020), which follow a trend from the inferior medial to superior brain regions (Calderon-Garcidueñas & Duyckaerts, 2018; Thal et al., 2014), and this pattern may be more pronounced in individuals with Aβ burden (Tian et al., 2023). In a largely preclinical sample, negative relationships were observed between NDI and CSF p-tau and CSF p-tau/Aβ42 (Moody et al., 2022). In contrast to CSF p-tau/Aβ42 associations, the relationship with CSF p-tau did not remain significant when removing AD and MCI participants from the analysis. In the same study, a positive relationship was observed between NDI and CSF Aβ42/40, remaining significant when removing AD and MCI participants (Moody et al., 2022). These results suggest that CSF Aβ42/40 and CSF p-tau/Aβ42 are more indicative of early white matter microstructural changes in axonal packing density.

ODI has shown various associations with AD biomarkers. Across the AD spectrum, ODI showed a consistent positive correlation with CSF p-tau/Aβ42, even after excluding AD and

MCI participants. In contrast, the correlation between ODI and CSF p-tau was not significant once AD and MCI participants were removed. Unlike NDI, ODI did not exhibit associations with CSF Aβ42/40 (Moody et al., 2022). Together, these findings suggest that among CSF biomarkers, only p-tau/Aβ42 is sensitive to early white matter microstructural changes in orientation dispersion. PET studies of tauopathy and amyloidosis have reported null findings when examining associations with ODI in the early stages of AD, suggesting that the overall organization of white matter tracts may not impacted (at least initially) despite a decrease in axonal packing density (Raghavan et al., 2021; Wen et al., 2021).

Few studies have investigated biomarker relationships with ISOVF. In a study involving a largely preclinical AD sample, no significant associations were found across AD spectrum with any of the CSF biomarkers of AD pathology (i.e., p-tau/Aβ42, p-tau, Aβ42/40) (Moody et al., 2022). ISOVF associations have been noted with both Aβ-PET and tau-PET across the AD spectrum (cognitively unimpaired, MCI, dementia). Higher levels of Aβ deposition were related to global increases in ISOVF, whereas higher levels of tau deposition were more specifically related to ISOVF increases in the inferior temporal white matter (Raghavan et al., 2021).

Having reviewed the literature on demographic, genetic, and biomarker associations with NODDI measures of white matter structural integrity, next I will review the potential mechanisms underlying these associations. Specifically, I will characterize how each NODDI measure may be influenced by white matter pathophysiology over the course of disease. In the final section, I will move beyond neurobiological factors to examine associations between NODDI and cognitive performance in aging and AD.

PATHOLOGICAL MECHANISMS OF CHANGE IN NODDI METRICS

Various pathological mechanisms have been suggested to explain the variations in white matter diffusion observed in typical aging and AD. Both human and animal studies of AD have observed that dMRI metrics demonstrate non-linear associations in response to Aβ accumulation in white matter (Dong et al., 2020; Fick et al., 2017; Wolf et al., 2015). This non-linear pattern is characterized by greater diffusion restriction at moderate Aβ levels and reduced restriction at higher levels. The findings suggest that distinct microstructural changes occur at different stages of the disease, where earlier stages may involve neuroinflammation, and subsequent stages marked by neurodegeneration.

Given that NDI is a measure of intra-axonal water, loss of neurons would lead to an increase in the extra-neurite space leading to reductions in neurite density (Motovylyak et al., 2022), as confirmed by post-mortem histological analysis (Slattery et al., 2017). In older adults, global NDI reductions have been observed in relation to increased white matter hyperintensities (Raghavan et al., 2021), suggestive of the contribution of vascular and neuroinflammatory factors on axonal packing density (Huang et al., 2022; Solé-Guardia et al., 2023). In AD, NDI decreases can result from the reduction or loss of cholinergic neurons and axons in the white matter due to Aβ deposition (Bellucci et al., 2006; Kar et al., 2004). Similarly, myelin degeneration, which has recently been shown to lead to Aβ plaque formation (Depp et al., 2023), can result in increases in the extra-neurite space leading to neurite density reductions (Walker et al., 2023). More recently, the integrity of myelin-containing subcortical brain regions (i.e., locus coeruleus and ventral tegmental area) has been associated with brain-wide axonal packing density reductions in the same at-risk sample of cognitively unimpaired older adults examined in this dissertation. The authors suggested that the observed widespread NDI reductions in the brain

may be reflective of age- or AD-related atrophy of neuromelanin-containing cells (Wearn et al., 2024).

As previously mentioned, ODI has been observed to exhibit both increases and reductions in response to disease processes, depending on the architecture of the tract in question. Additionally, as discussed earlier, it is more difficult to link ODI to an underlying pathological process, such as demyelination, inflammation, or atrophy, compared to other NODDI metrics (Raghavan et al., 2021). It has been suggested that the loss of secondary crossing fibres, indexed by ODI reductions, might be caused by selective degeneration of certain axons in AD (Slattery et al., 2017). In animal models, ODI increases reflective of pathological changes in or near axons and dendritic processes, along with increased density of misoriented axonal and dendritic processes in white matter and the hippocampus, have been related to neuroinflammatory processes, such as increases in activated microglial cells as well as Aβ plaque-related structural changes (Colon-Perez et al., 2019).

ISOVF increases have been shown to reflect atrophy in response to cell shrinkage and decreased tissue volume fraction (Colgan et al., 2016; Merluzzi et al., 2016), perhaps secondary to tau protein deposition (Fu et al., 2020). An increase in free water (Kraguljac et al., 2021), indexed by ISOVF, may also be reflective of expansion of the extracellular space in response to neuroinflammation (Syková & Nicholson, 2008).

NODDI ASSOCIATIONS WITH COGNITION ACROSS THE AD SPECTRUM

At the time of writing there were eight published reports investigating NODDI measures of white matter microstructure and associations with cognition across the AD spectrum. Initial results suggest that NODDI may be as effective (Raghavan et al., 2021; Wen et al., 2019), or superior to DTI in reflecting clinical cognitive status and ultimately AD diagnostic categories

(Fu et al., 2020). Across the AD spectrum, NDI has been associated with performance on screeners of global cognition such as the MMSE or MoCA (Tian et al., 2023). In contrast, DTI metrics have failed to show these associations (Fu et al., 2020). NDI reductions have also been related to reduced performance on a global cognition index and sub-domain scores of memory, attention, language, and visuospatial abilities across stages of AD progression, and these were stronger than ODI-cognition associations (Raghavan et al., 2021). In persons diagnosed with MCI, NDI was lower than that observed for cognitively unimpaired controls. These associations were stronger in the bilateral hippocampal cingulum (Gozdas et al., 2021; Wen et al., 2019) and the left uncinate fasciculus (Fu et al., 2020), tracts closely associated with episodic memory as well as the bilateral superior longitudinal fasciculus and the splenium of the corpus callosum (Fu et al., 2020).

In cognitively unimpaired individuals with familial AD-risk, reduced NDI was the most robust predictor of lower executive control abilities among both NODDI and DTI metrics. Specifically, NDI in the cingulum-corpus callosum was positively associated with executive control abilities, even when accounting for age, sex, APOE e4 genotype, and education (Motovylyak et al., 2022). In another sample that was enriched for AD risk via parental history (72%), lower NDI was associated with worse performance on tasks of word-list learning and complex attention. However, the authors noted that these associations were observed only on a limited number of tests from a larger battery (not correcting for multiple comparisons) and NDI measures were restricted to frontal regions (Merluzzi et al., 2016).

Generally, ODI correlations with cognition have been shown to be either weaker than NDI or absent (Gozdas et al., 2021; Motovylyak et al., 2022; Raghavan et al., 2021; Slattery et al., 2017). However, in studies that include groups across the AD-spectrum, ODI appears to be

sensitive to performance on tests of episodic memory and cognitive screeners. For example, poorer neuropsychological performance on the RAVLT (verbal learning and memory task), and cognitive screeners such as the MoCA and MMSE was associated with higher ODI in three tracts of interest; left parahippocampal cingulum, forceps major, and left posterior thalamic radiation in individuals who are cognitively unimpaired, as well as in MCI (Wen et al., 2019). Similarly, ODI values of the left superior longitudinal fasciculus were associated with MMSE and MoCA scores across the AD spectrum (i.e., combined group of cognitively unimpaired, MCI, and AD-dementia) in contrast to null FA findings (Fu et al., 2020).

As noted throughout the general discussion, very few studies have examined ISOVF associations in AD. However, several significant associations with cognition have been reported. ISOVF has shown significant associations with cognitive screeners, in comparison to FA (Fu et al., 2020). In another study that combined groups across the AD spectrum (80% cognitively unimpaired), ISOVF reduction in the corpus callosum was among the strongest predictors of slower sequencing performance on Trails B and global cognitive decline (Raghavan et al., 2021). No ISOVF-cognition associations were observed in cognitively unimpaired individuals with familial AD risk (Motovylyak et al., 2022).

Overview of Dissertation Research Program

This review suggests that microstructural changes in white matter are associated with AD risk and progression (Caso et al., 2016; Nasrabady et al., 2018), with evidence that alterations in white matter microstructure may be measurable before grey matter changes (Agosta et al., 2011; Amlien & Fjell, 2014; Canu et al., 2010; Maier-Hein et al., 2015; Parker et al., 2022; Salat et al., 2010; Stone et al., 2021; Stricker et al., 2013). Established disease risk factors, such as advancing age, APOE4 genotype, and family history, independently and conjointly influence white matter

integrity and the development of AD symptoms (Kamiya et al., 2020). Advances in *in vivo* neuroimaging approaches have furthered our understanding of the pathophysiology of white matter damage in AD, providing non-invasive methods to characterize disease-related changes across all disease stages. However, conventional diffusion-weighted imaging techniques such as DTI have been limited by low specificity for individual tissue characteristics and variable sensitivity across fibre tracts. Moreover, the validity of DTI metrics may be confounded by partial volume effects as well as complex fibre orientations, leading to potentially spurious findings.

Recent advances in diffusion-weighted imaging, including multi-shell diffusion MRI and NODDI modeling, offer a non-invasive approach to characterize white matter microstructure and axonal morphology *in vivo* that is more biologically plausible. NODDI shows greater sensitivity than traditional DTI metrics in both typical aging (Beck et al., 2021; Guerreri et al., 2019; Ota et al., 2017) and AD populations (Fu et al., 2020; Moody et al., 2022). Moreover, multi-shell DWI with NODDI modelling may have better predictive ability (Raghavan et al., 2021; Wen et al., 2019) than DTI for general cognitive status as well as more specific domains of cognitive performance as necessary for AD diagnosis and staging (Fu et al., 2020).

Finally, in addition to these demographic and genetic factors, the presence of AD-related pathologies are biomarkers for elevated AD-risk. Only two studies using NODDI metrics to investigate structural brain changes in preclinical AD have focused on positive AD biomarkers to index AD risk (Moody et al., 2022; Raghavan et al., 2021). However, the presence of AD pathology is not sufficient to predict the emergence of a clinical syndrome, and these biological risk markers likely interact with demographic and genetic risk factors to influence the

neurobiological changes, including white matter pathology, that ultimately determine the likelihood and speed of transitioning to the clinical syndrome.

In this dissertation, I investigated the impact of major demographic, genetic, and neuropathological AD risk factors on the microstructural integrity of white matter in a sample of older adults at elevated risk for AD, but who remain asymptomatic (for expediency, I will refer to this cohort as 'preclinical' in this dissertation). Specifically, I assessed differences in the three primary NODDI metrics as a function of the primary AD risk factors (Kamiya et al., 2020): (i) age (ii) genetics and (iii) biomarkers of AD pathology derived from PET imaging and CSF (Study 1) and associations with cognition (Study 2). Finally, early explorations of axonal morphology in the context of preclinical AD have been limited by reliance on univariate methods and have restricted their investigations to a priori selected brain regions. However, even in the earliest disease stages, before the emergence of a clinical syndrome, microstructural changes are likely occurring across the cerebrum, as indicated by findings of global cerebral atrophy encompassing both white matter and grey matter (Moody et al., 2022). Importantly, this has yet to be investigated using NODDI metrics. To address this challenge, here I use multivariate analysis methods to investigate whole brain associations between white matter microstructure, AD risk factors, and cognition in a large cohort of older adults at elevated disease risk.

CHAPTER 2

Study 1: Assessing White Matter Microstructure in the Context of Demographic, Genetic, and Neuropathological Risk Factors in Preclinical Alzheimer's Disease

AD progression is characterized by the accumulation of Aβ plaques (Ikonomovic et al., 2008; Klunk et al., 2004; Nordberg, 2004) and tau tangles in the brain (Alonso et al., 1996). This neuropathological course, which denotes the preclinical stage of AD, begins decades before clinical symptom onset and the appearance of any observable cognitive changes (Dubois et al., 2010; Sperling et al., 2011). CSF and PET biomarkers of amyloidosis and neurofibrillary tau tangles support *in vivo* tracking of these neuropathological changes (Jack et al., 2018). Although accumulation of Aβ and tau pathology is necessary for the development of AD preclinically, it is not enough to lead to progression towards clinical symptoms. The emergence of clinical symptoms is marked by neurodegeneration, including connectivity alternations in white matter (Fischer et al., 2015; Hoy et al., 2017) which have been shown to precede grey matter change (Agosta et al., 2011; Amlien & Fjell, 2014; Canu et al., 2010; Maier-Hein et al., 2015; Parker et al., 2022; Salat et al., 2010; Stone et al., 2021; Stricker et al., 2013). In these early disease stages, white matter changes are subtle and only observable at the microstructural level (Alm & Bakker, 2019).

Diffusion-weighted imaging techniques have supported non-invasive and *in vivo* investigations of white matter microstructure in the human brain that precede overt cell loss (Le Bihan et al., 1986). Findings from DTI (the most conventional diffusion imaging method) suggest that aging is associated with white matter abnormalities characterized by decreased FA, increased MD (Wassenaar et al., 2019), and increased RD (Bennett & Madden, 2014; Cox et al., 2016; de Groot et al., 2015) (please see Chapter One for an overview of these metrics). These

changes begin between ages 30-50 (Kochunov et al., 2012; Lebel et al., 2012; Sexton et al., 2014), become more pronounced with advancing age (Sexton et al., 2014), and may predict progression to prodromal disease stages (Ten Kate et al., 2018). In preclinical stages, white matter changes are particularly noted in the corpus callosum and limbic tracts such as the posterior and parahippocampal cingulum, uncinate fasciculus, and fornix (Gold et al., 2012; Mielke et al., 2009; Nowrangi et al., 2013). These changes appear years prior to grey matter or cognitive changes (Teipel et al., 2016), can be more pronounced in APOE4 carriers (Lopez et al., 2003; Petersen et al., 2014; Ungar et al., 2014), and are linked to disease severity and progression, with distinct patterns of diffusivity associated with Aβ pathology (indexed by lower CSF Aβ42 levels) (Alm & Bakker, 2019) and high neurofibrillary tangle aggregation (indexed by higher CSF p-tau or t-tau levels) (Kantarci et al., 2017; Stenset et al., 2011). Studies implementing PET indices of Aβ deposition have also shown non-linear associations, wherein white matter may first exhibit compensatory changes in response to early Aβ pathology, marked by increased FA and decreased diffusivity measures (MD, AD, RD), followed by axonal degeneration in the context of further Aβ accumulation, associated with FA decreases and increases in diffusivity measures (Collij et al., 2021; Dong et al., 2020; Wolf et al., 2015).

NODDI is a novel diffusion-weighted imaging analytical approach based on a biophysical model. NODDI supports more specific, sensitive, and clinically efficient detection of changes in tissue cytoarchitecture than the more commonly reported DTI-based measures (Timmers et al., 2016; Zhang et al., 2012). Several NODDI studies have now provided evidence of altered white matter microstructural integrity and axonal morphology in typical aging and AD. In typical aging, NODDI metrics reveal complex trajectories: The neurite density index (NDI), increases until age 40 at which point it begins to decline, with more rapid decreases in the 50-

60s, suggesting early widespread loss of axonal packing density (Beck et al., 2021; Cox et al., 2016; Gozdas et al., 2021; Qian et al., 2020). In atypical aging, NDI is emerging as a robust marker for AD-related changes, with preliminary studies demonstrating declines that correlate with disease severity and alterations in tau and Aβ deposition (Colon-Perez et al., 2019; Fu et al., 2020; Gozdas et al., 2021; Moody et al., 2022; Slattery et al., 2017; Tian et al., 2023; Wen et al., 2021). The orientation dispersion index (ODI) exhibits varied region-dependant patterns, and appears to be largely influenced by the architecture and trajectory of specific white matter tracts (Cox et al., 2016; Kodiweera et al., 2016; Raghavan et al., 2021). The isotropic volume fraction (ISOVF) consistently increases with age (Beck et al., 2021; Billiet et al., 2015; Guerreri et al., 2019; Merluzzi et al., 2016; Raghavan et al., 2021), likely due to higher interstitial water in the extracellular space (Chad et al., 2018; Meier-Ruge et al., 1992). Increases in ISOVF are also associated with greater disease severity across different stages of AD (Fu et al., 2020; Motovylyak et al., 2022), though associations with AD biomarkers have yet to be comprehensively investigated.

Overall, preliminary implementations of the NODDI approach highlight its potential to detect subtle changes in white matter microstructure across the aging spectrum and in the context of AD pathology. However, very few studies have reported NODDI changes in at-risk, preclinical AD cohorts due to a limited focus on these early-stage samples, and the early characterization of whole-brain white matter microstructure in AD remains unclear. Only two studies to date have applied NODDI techniques in at-risk individuals as indexed by positive AD pathological biomarkers (Moody et al., 2022; Raghavan et al., 2021). However, AD pathology alone does not predict clinical symptom onset, as this approach neglects the interacting risk factors influencing progression from preclinical to clinical stages. In addition to age and

biomarkers of disease pathology, examining factors such as APOE genotype and family history is critical for understanding early white matter changes in AD.

APOE4, the strongest genetic risk factor for AD (Saunders et al., 1993), disrupts cholesterol regulation, consequently impairing white matter repair (Bartzokis, 2011; Blanchard et al., 2022), resulting in Aβ plaque aggregation (Lesser et al., 2011). This cycle leads to a greater risk of AD and white matter degeneration even in cognitively unimpaired individuals (Bagepally et al., 2012; Cai et al., 2017; Cavedo et al., 2017; Douaud et al., 2011; Dowell et al., 2013; Gold et al., 2010; Heise et al., 2014; Nierenberg et al., 2005; Persson, Lind, et al., 2006). Family history also increases AD risk (Breitner et al., 1999; Huang et al., 2004), with first-degree relatives being 4-10 times more likely to develop the disease (Cupples et al., 2004; Green et al., 2002; Silverman et al., 2005). NODDI studies have shown that white matter changes are more pronounced with advancing age in cognitively unimpaired individuals with a family history of AD (Merluzzi et al., 2016; Motovylyak et al., 2022), but how these changes interact with genetic risk and AD pathology remains unclear.

In Study 1 of the dissertation, I address this gap by examining age, APOE4 genotype, and AD biomarkers in a single cohort of individuals with a family history of AD to identify how each of these factors is associated with white matter microstructure, indexed by the three NODDI metrics (see Chapter One for a review). Elevated familial risk was determined based on specific inclusion criteria for the cohort. All participants have a parental or multi-sibling history of AD, with age of parent/sibling diagnosis occurring within 10 years of participant age at study enrolment. Given that first-degree relatives are at a significantly higher risk than those with more distant familial connections (Cupples et al., 2004; Green et al., 2002; Silverman et al., 2005), this unique cohort enabled me to examine associations between white matter microstructure, age,

genetics, and biomarkers of AD pathology in the context of elevated disease risk and in the absence of clinical symptoms (see Methods). With respect to analyses, I applied a data-driven multivariate analytical model to examine whole-brain white matter microstructure in relation to markers of AD-disease risk. My approach includes whole-brain characterization of white matter given that the literature to-date has often limited investigations to a restricted number of tracts rather than examining brain-wide patterns. To examine white matter microstructure and axonal morphology, I quantified all three NODDI metrics, given that ISOVF has often been overlooked in the AD literature. These indices were then examined in the context of advancing age, APOE4 status, CSF biomarkers (Aβ42, t-tau, p-tau, t-tau/Aβ42, p-tau/Aβ42), and PET biomarkers (Aβ and tau).

Based on past literature, I predicted that with increased AD risk based on older age and increased abnormalities in AD biomarkers: (1) NDI in white matter would decrease, reflecting reduced axonal packing density; (2) ODI in white matter would decrease in architecturally complex tracts, reflecting selective loss of crossing fibers. ODI would increase in more uniform tracts, reflecting increased loosening, fanning, and decreased fiber alignment; (3) ISOVF would increase, reflecting an increase in non-constrained free water due to sparser tissue structure.

Methods

Participants

One hundred and forty-six participants with first-degree family history of AD were included in this study (71.9% female; Mage = 68.12; age range: 57–85). See Table 2.1 for sample demographics. Participants were selected from Preclinical EValuation of Experimental or Novel Treatments for AD (PREVENT-AD) cohort (Tremblay-Mercier et al., 2021) recruited through media and community advertisements across Montreal and surrounding areas in Quebec,

Canada. For more information about PREVENT-AD the reader is directed here: http://prevent-alzheimer.net. All study participants provided informed written consent prior to study participation. The procedures of the PREVENT-AD study were administered in compliance with the McGill institutional review board and/or the Douglas Mental Health University Institute Research Ethics Board. Additional approval for the current dissertation was provided by the institutional review board at York University. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

As noted above, all participants were at elevated familial risk for AD. The cohort underwent genotyping and was tracked through naturalistic studies assessing cognition, neurosensory capacities (i.e., smell identification and auditory processing), CSF biochemistry, MRI, and medical and clinical evaluations. Of the 146 participants included in this dissertation, all had multi-shell diffusion MRI and genetic data, 99 had a lumbar puncture to extract CSF, and 128 were scanned with Aβ-PET and tau-PET radio tracers (see Table 2.1).

Table 2.1
Sample demographics (n=146)

	n	**%**
Gender		
Female	105	71.9
Male	41	28.1
Race/Ethnicity		
Caucasian	145	99.32
African Canadian	1	0.68
Mother Tongue		
English	14	9.6
French	129	88.4
Italian	1	0.7
Other	2	1.4
APOE4 Carrier Status		
APOE4+	58	39.7
APOE4-	88	60.3

Aβ-PET status (*n*=128)				
Aβ+	39	30.5		
Aβ-	89	69.5		
Variable	**Minimum**	**Maximum**	**Mean**	**SD**
Education (years)	7	27	15.39	3.45
Age at time of MRI (years)	57.17	84.75	68.12	5.33
Time between CSF and MRI scans (months)	20	83	32.48	13.61
Time between PET and MRI scans (months)	2	42	23.43	8.22
Tau-PET (*n*=128)	0.97	1.69	1.16	0.10
CSF (pg/ml) (*n*=99)				
Aβ42	463.83	2762.09	1229.77	358.45
t-tau	79.53	1279.87	319.11	184.55
p-tau	19.91	156.83	55.16	22.04

Note. SD, standard deviation; CSF, cerebrospinal fluid; PET, positron emission tomography; MRI, magnetic resonance imaging; Aβ, beta-amyloid.

Neuroimaging Protocol

Methods related to the neuroimaging protocol, acquisition, and processing have been previously published (Wearn et al., 2024) and are reviewed briefly here. Neuroimaging data were collected using a 3T Siemens PrismaFit MRI scanner at the Douglas Research Centre. All participants underwent T1-weighted imaging and multi-shell diffusion MRI. T1-weighted anatomical scans were acquired using a 3-dimensional magnetization rapid gradient echo (MPRAGE) sequence (1mm isotropic resolution, TR/TE/TI = 2300/2.96/900ms, FA = 9°, TA = 5:30). Multi-shell diffusion-weighted imaging employed a 2mm isotropic spin-echo echo-planar imaging sequence. A total of 109 diffusion-weighted directions were sampled, evenly distributed across three shells with the following diffusion weightings: 7 directions at b=300 s/mm², 29 at b=1000 s/mm², and 64 at b=2000 s/mm². Additionally, 9 b=0 images were acquired using a TR/TE of 3000/66 ms and posterior-to-anterior phase encoding. For distortion correction, an extra set of five b=0 images were collected using the same sequence parameters but with

reversed phase encoding (anterior-to-posterior). The complete acquisition time for the sequence was 5 minutes and 49 seconds. All imaging sequences provided complete coverage of the brain and encompassed the brainstem.

Neurite Orientation Dispersion and Density Imaging

Neurite orientation dispersion and density imaging (NODDI) was used to assess white matter microstructure (Zhang et al., 2012). NODDI relies on multi-shell diffusion encoding and a multi-compartment biophysical model of brain tissue which enables it to provide more specific and clinically meaningful parameters.

NODDI Processing

MRtrix3 toolbox was used to preprocess all diffusion data (Tournier et al., 2019). Preprocessing steps included denoising (*dwidenoise*) (Cordero-Grande et al., 2019; Veraart, Fieremans, et al., 2016; Veraart, Novikov, et al., 2016), as well as correction for eddy current distortion, susceptibility artifacts, and motion artifacts (*dwifslpreproc*) (Andersson et al., 2003; Andersson & Sotiropoulos, 2016; Smith et al., 2004). Images were upsampled to 1mm isotropic resolution (*mrgrid*) and then underwent brain extraction (bet2) (Smith, 2002) and bias-field artifact correction with the ANTs algorithm (N4) (Tustison et al., 2010) of the *dwibiascorrect* MRtrix function. The NODDI model was fitted to the bias field corrected diffusion-weighted data using the Accelerated Microstructure Imaging via Convex Optimization (AMICO) implementation in Python (Daducci et al., 2015; Zhang et al., 2012). Response functions were calculated for each compartment. Model fitting was subsequently applied to the bias-corrected diffusion-weighted volumes restricted to the brain mask. The derived parameters include the neurite density index (NDI), the isotropic volume fraction (ISOVF), and the orientation dispersion index (ODI). NODDI metrics were examined across the whole brain white matter.

The *5ttgen* function of MRtrix3 was used to develop a probabilistic mask of normal-appearing white matter for each participant (Smith et al., 2012).

Normalization of NODDI Maps to MNI Space. Upsampled NODDI maps, along with probabilistic white-matter masks, were aligned to MPM maps using FSL's 'flirt' tool. This was done through rigid-body registration, where b=0 diffusion-weighted images served as the moving image and proton density (PD) maps were used as the reference due to their similar contrast properties. Next, MTsat maps were segmented into different tissue classes (i.e., grey matter and white matter). Deformation fields were then computed to convert the native brain space to the standardized MNI (2009c) space using the 'Shoot' toolbox in SPM12 (Ashburner & Friston, 2011). These deformation fields were subsequently used to transform the NODDI maps and white-matter masks into MNI template space. The MNI-warped white-matter masks were averaged across participants and thresholded at 0.95 to retain only regions with a 95% probability of being white matter. Images were then smoothed using a 1mm full-width half-maximum Gaussian kernel to enhance image quality. The derived images were used for partial least squares (PLS) analysis (described below).

Age Regressed Residual Images. A second set of NODDI data accounting for age was created to supplement each original NODDI map. This age-residualized dataset was developed to control for potential age-related variability in white matter metrics, given that age has been shown to have strong associations with white matter changes and a core study objective was to examine associations between genetic risk and neuropathological biomarkers and white matter microstructural integrity over and above age-related changes. Put simply, this approach allowed for the examination of specific relationships between NODDI measures and other AD risk markers without the confounding influence of age. Multiple regression was used to regress age

from the unsmoothed NODDI maps described above, implemented in SPM12. These age-residualized images were subsequently smoothed with a 1mm full-width half-maximum Gaussian kernel. The resulting residual images were input into the partial least squares (PLS) analyses (described below).

Alzheimer's Disease Risk Markers

Genotyping and methods for extracting CSF from participants has been described previously (Tremblay-Mercier et al., 2021) and are summarized below.

APOE4 Genotyping

DNA was extracted from 200 µl of whole blood using a standard QIASymphony apparatus and the DNA Blood Mini QIA Kit (Qiagen, Valencia, CA, USA), in compliance with the manufacturer's protocol. Allelic variants of APOE genes (rs429358 and rs7412) were identified using pyrosequencing (PyroMark24 or PyroMark96) or DNA microarray (Illumina). Due to the small proportion of e4/e4 carriers, individuals were identified as having zero e4 alleles (APOE4−) or as having at least one e4 allele (APOE4+). Of the 146 study participants, 58 people had at least one APOE4 allele and 88 did not. The higher ratio of carriers in our sample compared to the general population is due to the intentional recruitment of individuals with a familial risk of AD based on first-degree family history.

Cerebral Spinal Fluid (CSF) Biomarker Acquisition and Analysis

CSF samples of up to 30 ml were collected via lumbar puncture between the L3-L4 or L4-L5 intervertebral space using an atraumatic Sprotte 24 Ga. spinal needle. Lumbar punctures were performed by a neurologist (Dr. P. Rosa-Neto). Centrifugation of samples was performed at room temperature for 10 minutes at ~2000g. Samples were then frozen at −80°C for storage. CSF concentrations of amyloid-beta 1-42 (Aβ42), total tau (t-tau), and phosphorylated tau at

threonine 181 (p-tau) were measured with Innotest technology (Fujirebio) using enzyme-linked immunosorbent assay. CSF data were available for 99 participants. CSF was collected before MRI data, with a mean delay of 32.48 ± 13.61 months. To account for this, the time interval between CSF and MRI data collection was controlled for in statistical analyses where appropriate.

Positron Emission Tomography Processing

PET data was available for 128 participants. The processing procedures have been described previously (Qiu et al., 2024) and are summarized briefly here. Processing of PET images was completed using a standard pipeline from the Villeneuve lab at McGill University and the Douglas Research Centre headed by Dr. S. Villeneuve, the director of the PREVENT-AD program (see https://github.com/villeneuvelab/vlpp for more details). Aβ-PET and tau-PET scans were realigned, averaged, and co-registered to T1-weighted MRI images. To define regions of interest in each participant's native space, the T1 scans were first segmented and processed in FreeSurfer 5.3 based on the Desikan-Killiany atlas (Desikan et al., 2006). The registered PET images were then masked to remove CSF signal and smoothed using a Gaussian kernel of 6 mm^3. To compute the standardized uptake value ratios (SUVRs), the cerebellum cortex was used as a reference region for Aβ-PET images (Jagust et al., 2015), and the inferior cerebellar grey matter was used for tau-PET images (Baker et al., 2017). A whole-brain index of Aβ burden was created by averaging the SUVR values across the bilateral medial and lateral frontal, parietal, and temporal regions following previously reported methods (Pichet Binette et al., 2021). A Gaussian mixture model was used to determine an amyloid-positive threshold cut-off point of 1.30 (De Meyer et al., 2010). This quantitative approach has been shown to be more robust than clinical diagnosis in detecting AD-related biological changes (Bertens et al., 2017).

Based on this cut-off point, 39/128 participants were classified as beta-amyloid positive (Aβ+) and 89/128 participants were classified as beta-amyloid negative (Aβ-). Among PET participants who were APOE4 carriers, 23 were classified as Aβ+. Among PET participants who were APOE4 non-carriers, 16 were classified as Aβ+. The breakdown of participants per group were as follows: APOE4+ Aβ+ (n = 23), APOE4+ Aβ- (n = 29), APOE4- Aβ+ (n = 16), APOE4- Aβ- (n = 60). The assessment of tau pathology included generation of a whole-brain index of tau burden using a temporal meta-region of interest (meta-ROI). This was done by calculating the mean SUVR of the bilateral entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal regions (Jack Jr et al., 2017). Tau-PET data was treated as continuous in all dissertation analyses.

Statistical Analysis

A preliminary analysis was conducted to examine associations between demographic and behavioural variables in this sample. Pearson correlations were calculated to assess the associations between age, education, and AD biomarkers (i.e., CSF and PET data), with 1000 bootstrapped samples used to compute confidence intervals. Partial Least Squares (PLS) was performed to identify associations between NODDI metrics (NDI, ODI, ISOVF) and AD risk factors (age, APOE4 status, CSF biochemistry, PET biomarkers) (McIntosh & Lobaugh, 2004; McIntosh & Mišić, 2013). PLS is a data-driven, multivariate statistical technique that allows for the identification of patterns between whole-brain microstructure and behavioural variables. For this reason, it was considered the preferred method of analysis for this study. Age, CSF risk factors, and Tau-PET were treated as behavioral variables and were each independently examined in separate behavioral PLS (bPLS) analyses, with only one NODDI metric and one behavioral variable included per model. Given their categorical nature, APOE4 status and Aβ-

PET status were treated as grouping variables and were examined with each NODDI metric using mean-centering PLS analyses. Permutation tests of 1000 samples were used to evaluate the significance of the brain-wide data of each NODDI metric associated with each AD risk factor captured by a given latent variable (LV), while 1000 bootstrap samples were used to determine the reliability of the observed effects. 'Bootstrap ratios' (BSRs) are equivalent to z-scores if the sampling distribution is approximately unit normal (Efron & Tibshirani, 1986). Brain region patterns were considered reliable if the absolute value of the BSR exceeded ±1.98 (approximately $p < 0.05$).

PLS supports identification of covariance patterns between several variables in a single model and a single analytic step without the need for multiple-comparisons correction. Each NODDI-parameter had two maps, one original and one age-regressed. Significant PLS associations between the original NODDI map and an AD risk factor were re-analyzed a second time with the age-residualized maps to examine these patterns when the effects of age were accounted for. All PLS analyses were performed in MATLAB R2021a (Mathworks Inc.) (McIntosh & Lobaugh, 2004).

To assist with visual identification of white matter pathways, the JHU white-matter tractography atlas (Hua et al., 2008) was referenced for each statistically significant pattern identified by PLS. The JHU atlas is a 20-structure overlay map in MNI space and is currently the most commonly used white matter template in the literature (Chen et al., 2023). For enhanced visualization, all brain images were more stringently thresholded to ±2.57 (approximately $p < 0.01$).

Follow-up Partial Correlation Analyses

The brain score is a composite score representing the extent to which each participant expresses the group LV pattern in PLS. Where appropriate, brain scores from PLS analyses were extracted to examine their associations with study variables. Specifically, partial correlations were computed in SPSS version 29 with a 95% confidence interval (CI) based on 1000 bootstrap samples. Statistical significance was set at $p < 0.05$, utilizing a two-tailed approach. All partial correlation analyses controlled for the effects of participant gender and education, and where appropriate, participant age, APOE4 status, time between DWI and PET scans, and time between DWI and CSF collection.

Results

Assessing Collinearity Among Independent Variables

I first assessed associations among all independent variables to aid interpretation of the multivariate association patterns with NODDI metrics. Specifically, Pearson correlation and CI's based on 1000 bootstrapped samples were calculated to assess associations between age, education, and AD biomarkers. P-values reported in Table 2.2 were Bonferroni corrected for multiple comparisons (shown as p_{adj}). As predicted, CSF p-tau and CSF t-tau were found to be strongly positively correlated ($r(97) = .96$, 95% CI [.93, .98], $p_{adj} < .001$). A positive association was identified between tau-PET and age ($r(126) = .25$, 95% CI [.09, .42], $p = .02$). Tau-PET was also positively correlated with CSF t-tau $r(84) = .36$, 95% CI [.03, .59], $p < .001$) and CSF p-tau $r(84) = .36$, $p < .001$, 95% CI [.05, .59]). No other significant correlations were noted between covariates (see Tables 2.2-2.4).

Table 2.2
Pearson Correlation Matrix of CSF Biomarkers and Demographics (n=99)

	Education	Age	CSF t-tau	CSF p-tau	CSF Aβ42
Education	-				
Age	-.03 [-.25, .17]	-			
CSF t-tau	-.10 [-.30, .07]	-.03 [-.21, .14]	-		
CSF p-tau	-.12 [-.31, .07]	-.01 [-.20, .18]	.96** [.93, .98]	-	
CSF Aβ42	.17 [-.01, .38]	-.06 [-.24, .13]	-.02 [-0.22, .19]	-.01 [-0.23, .23]	-

Note. Parenthetical values indicate the 95% confidence interval for each correlation. CI's are based on 1000 bootstrap samples. *p < .05; **p < .01.

Table 2.3
Pearson Correlation Matrix of Tau-PET and Demographics (n=128)

	Education	Age
Tau-PET	.06 [-.11, .25]	.25* [.09, .42]

Note. Parenthetical values indicate the 95% confidence interval for each correlation. CI's are based on 1000 bootstrap samples.
*p < .05; **p < .01

Table 2.4
Pearson Correlation Matrix of Tau-PET and CSF Biomarkers (n=86)

	CSF t-tau	CSF p-tau	CSF Aβ42
Tau-PET	.36** [.03, .59]	.36** [.05, .59]	-.14 [-.36, .12]

Note. Parenthetical values indicate the 95% confidence interval for each correlation. CI's are based on 1000 bootstrap samples.
*p < .05; **p < .01

White Matter Microstructure and Markers of AD Risk in Preclinical AD

To investigate how white matter microstructure in preclinical AD relates to established markers of disease risk, all three NODDI metrics (NDI, ODI, ISOVF) were calculated to characterize whole-brain white matter. PLS was then used to determine multivariate associations between NODDI metrics and established markers of disease risk (age, APOE4 carrier status, CSF biomarkers, and PET biomarkers).

White Matter Microstructure and Age

Age significantly covaried with all three NODDI metrics. As predicted, for NDI, a pattern of reduced NDI values in the context of increasing age was observed across large areas of white matter (Figure 2.1B). Brain scores, representing the degree to which each individual expressed the NDI latent variable pattern, were significantly and positively associated with age (r = .39, 95% CI [.29, .48], permuted $p < .001$), demonstrating that older age was more robustly associated with lower axonal packing density (i.e. NDI). This pattern was observed across limbic and association fibres along with commissural and projection fibres, most prominently in the uncinate fasciculus on the right and bilaterally in the forceps minor, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, anterior thalamic radiations (R>L), corticospinal tract, and cerebellum (Figure 2.1B; see Appendix D for MNI coordinates). This finding remained significant when excluding a multivariate (i.e., PLS) outlier from the analysis age (r = .37, 95% CI [.29, .48], permuted $p < .001$; Figure 2.1A).

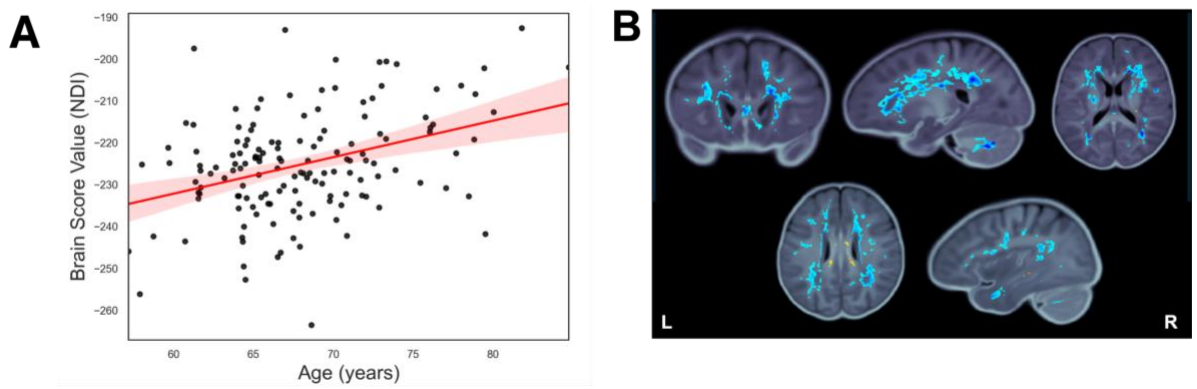

Figure 2.1. A significant association was observed between the Neurite Density Index (NDI) and age (panel A). This association was observed in the right uncinate fasciculus, and bilaterally in the forceps minor, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, anterior thalamic radiations (R>L), corticospinal tract, and cerebellum (panel B). With increasing age, neurite density decreases. This finding remained significant when excluding an outlier from the analysis, as pictured here.

For ODI, a mixed pattern of positive and negative associations was observed with age across the brain (Figure 2.2B). Brain scores associated with this pattern were highly positively associated with participant age (r = .68, 95% CI [.62, .73], permuted p < .001). The whole-brain pattern was characterized by age-associated ODI reductions bilaterally in the corticospinal tract, inferior fronto-occipital fasciculus, anterior thalamic radiations. In addition, ODI increases in the context of increasing age were observed in the forceps minor bilaterally (Figure 2.2B; see Appendix E for MNI coordinates). This finding remained unchanged when excluding a multivariate outlier from the analysis (r = .68, 95% CI [.62, .73], permuted p < .001; Figure 2.2A).

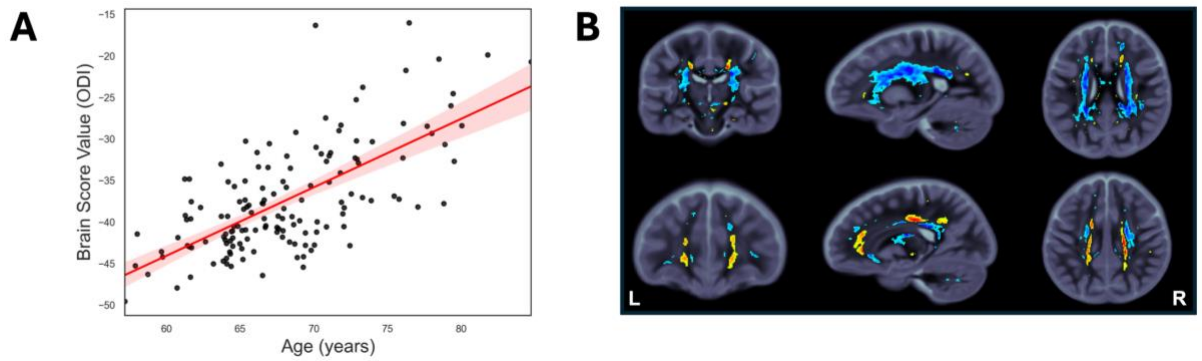

Figure 2.2. A significant association was observed between age and the Orientation Dispersion Index (ODI) (panel A). With advancing age, axonal orientation dispersion decreases bilaterally in the corticospinal tract, inferior fronto-occipital fasciculus, and anterior thalamic radiations (cool colours), and increases in the forceps minor bilaterally (warm colours) (panel B). This finding remained unchanged when excluding an outlier from the analysis, as pictured here.

For ISOVF, as predicted, a diffuse pattern of positive associations was observed with age (Figure 2.3B). Brain scores associated with this pattern were strongly and positively correlated with age (r = .76, 95% CI [.67, .85], permuted p < .001), consistent with predictions that increasing age is associated with increasing interstitial free water. Age-ISOVF associations were observed bilaterally in the cingulum, forceps minor, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract on the right (Figure 2.3B; top panel; see Appendix F for MNI coordinates), as well a select number of tracts proximal to the superior longitudinal fasciculus and corticospinal tract that could not be identified with the JHU atlas (Figure 2.4B; bottom panel). This finding remained significant when excluding a multivariate outlier from the analysis (r = .81, 95% CI [.75, .87], permuted p < .001, Figure 2.3A).

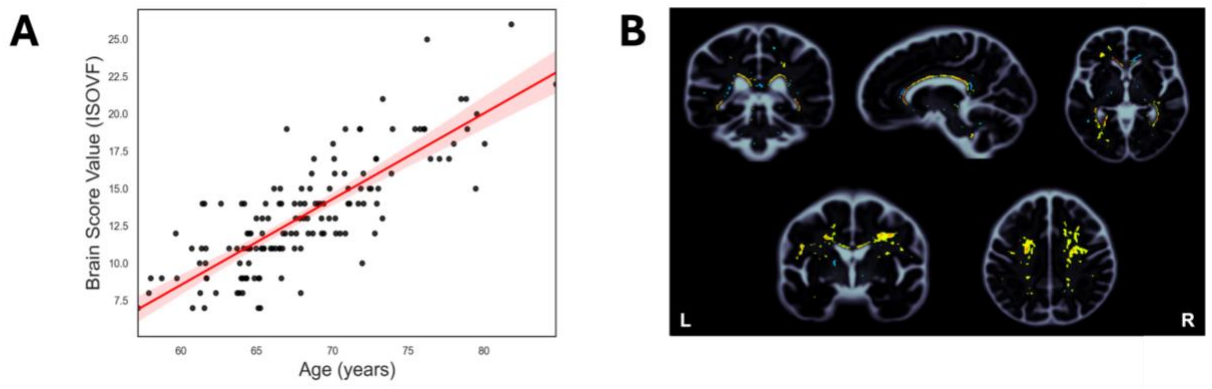

Figure 2.3. A significant association was observed between age and the Isotropic Volume Fraction (ISOVF) (panel A). This association was observed bilaterally in the cingulum, forceps minor, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract on the right (panel B, top row) and select fibre bundles proximal to the superior longitudinal fasciculus and corticospinal tract that could not be identified with the JHU atlas (panel B, bottom row). With increasing age, free water increases. This finding remained significant when excluding an outlier from the data, as pictured here.

White Matter Microstructure and Genotype

No significant associations were observed between APOE4 carrier status and any NODDI measure. Specifically, APOE4+ and APOE4- individuals did not significantly differ in white matter neurite density (NDI: LV1 p = .201, LV2 p = .903), orientation dispersion (ODI: LV1 p = .795, LV2 p = .159), or free water fraction (ISOVF: LV1 p = .671, LV2 p = .579). Moreover, these results were not altered whether participant age was included or regressed out of the model (NDI: LV1 p = .415, LV2 p = .829; ODI: LV1 p = .915, LV2 p = .979; ISOVF: LV1 p = .425, LV2 p = .752).

White Matter Microstructure and CSF-derived AD Biomarkers

CSF Aβ42. There was a significant association between CSF Aβ42 and NDI (r = .33, 95% CI [.14, .53], permuted p = .026). Such that, with lower levels of circulating Aβ42 (i.e., increased amyloidosis), axonal packing density decreases in the right forceps minor, left forceps major, right anterior thalamic radiation, and left superior longitudinal fasciculus (not pictured).

This finding remained significant when accounting for the effects of age (r = .36, 95% CI [.17, .55], permuted p = .025; Figure 2.4). See Appendix A for the original non-age residualized figures and Appendix G for MNI coordinates.

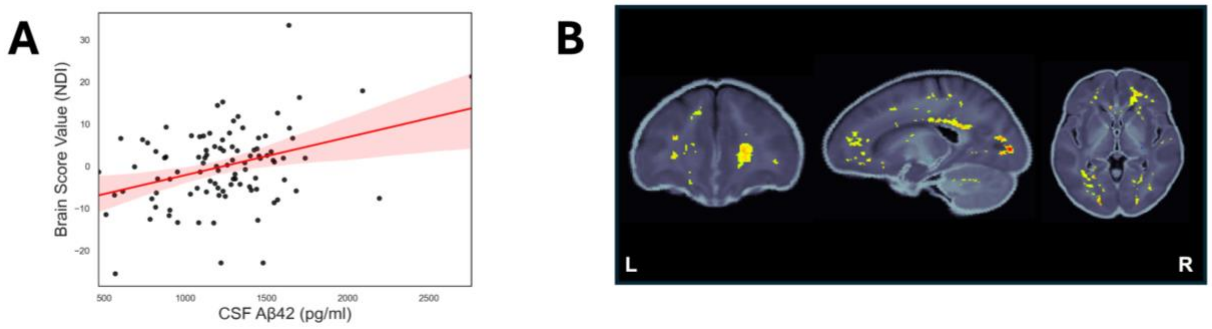

Figure 2.4. A significant association was observed between the Neurite Density Index (NDI) and CSF Aβ42 concentration (pg/ml) (panel A), this association was observed in the right forceps minor, left forceps major, right anterior thalamic radiation, and left superior longitudinal fasciculus (not pictured) (panel B). Axonal packing density reduces with lower circulating Aβ42 (i.e., increased amyloidosis). This association remains significant when accounting for the effects of age, as pictured here in the age-residualized images.

By contrast, CSF Aβ42 did not exhibit any significant associations with ODI (r = .90, 95% CI [.82, .98], permuted p = .388) or ISOVF (r = .85, 95% CI [.75, .94], permuted p = .274).

CSF t-tau. No associations were observed between NODDI metrics and CSF t-tau (NDI: r = .32, 95% CI [-.00, .64], permuted p = .602; ODI: r = .71, 95% CI [.60, .82], permuted p = .181; ISOVF: r = .89, 95% CI [.81, .98], permuted p = .599).

CSF p-tau. Similarly, there were no significant associations between NODDI metrics and CSF p-tau (NDI: r = .36, 95% CI [.03, .69], permuted p = .76; ODI: r = .72, 95% CI [.62, .82], permuted p = .225; ISOVF: r = .89, 95% CI [.81, .98], permuted p = .695).

CSF t-tau/Aβ42. No associations were observed between NODDI metrics and CSF t-tau/Aβ42 (NDI: r = .43, 95% CI [.12, .73], permuted p = .60; ODI: r = .83, 95% CI [.73, .92], permuted p = .477; ISOVF: r = .85, 95% CI [.76, .93], permuted p = .144).

CSF p-tau/Aβ42. Likewise, there were no significant associations between NODDI metrics and CSF p-tau/Aβ42 (NDI: r = .37, 95% CI [.05, .68], permuted p = .389; ODI: r = .87, 95% CI [.79, .97], permuted p = .62; ISOVF: r = .84, 95% CI [.75, .92], permuted p = .075).

White Matter Microstructure and PET-Derived AD Biomarkers

There were no significant associations between Aβ-PET pathological markers with NDI (LV1 permuted p = .518, LV2 permuted p = .283), ODI (LV1 permuted p = .078, LV2 permuted p = .681), or ISOVF (LV1 permuted p = .543, LV2 permuted p = .905), indicating that Aβ-PET+ and Aβ-PET- individuals did not differ in metrics of axonal packing density, orientation dispersion, or free water volume. Similarly, there were no significant relationships between tau-PET and NODDI metrics (NDI: r = .29, 95% CI [.05, .54], permuted p = 1.00; ODI: r = .78, 95% CI [.68, .88], permuted p = .406; ISOVF: r = .80, 95% CI [.71, .90], permuted p = .130). Finally, when the cohort was divided into Aβ-PET+ and Aβ-PET- individuals, no significant associations between tau-PET pathology and NDI (LV1 permuted p = .639, LV2 permuted p = .520), ODI (LV1 permuted p = .668, LV2 permuted p = .131), or ISOVF (LV1 permuted p = .898, LV2 permuted p = .180) were observed for either group.

White Matter Microstructure, PET-Derived AD Biomarkers, and Genetic Risk

To further characterize white matter microstructure in the context of AD pathology and genetic risk, I examined NODDI metrics differentiating individuals based on both Aβ-PET status and APOE4 carrier status. This analysis included four groups: APOE4+ Aβ+ (n = 23), APOE4+ Aβ- (n = 29), APOE4- Aβ+ (n = 16), APOE4- Aβ- (n = 60). PLS identified one significant latent variable that explained 51.86% of the variance between APOE4/Aβ-PET status and NDI (permuted p = .029). This pattern differentiated white matter microstructural integrity in the APOE4+ Aβ- group from the APOE4- Aβ+ and APOE4- Aβ- groups. Specifically, APOE4

carriers who remained Aβ- showed significantly lower axonal packing density bilaterally in the superior longitudinal fasciculus, inferior longitudinal fasciculus (not pictured), forceps minor, and left corticospinal tract when compared to individuals who are APOE4-, regardless of their Aβ status. This pattern remained significant even when the group with the smallest sample (APOE4- Aβ+) was removed from the analysis (74.31% variance explained, permuted p = .031) as well as when accounting for age in the age-residualized analysis (56.86% variance explained, permuted p = .007; Figure 2.5). See Appendix B for original non-age residualized figure and Appendix H for MNI coordinates.

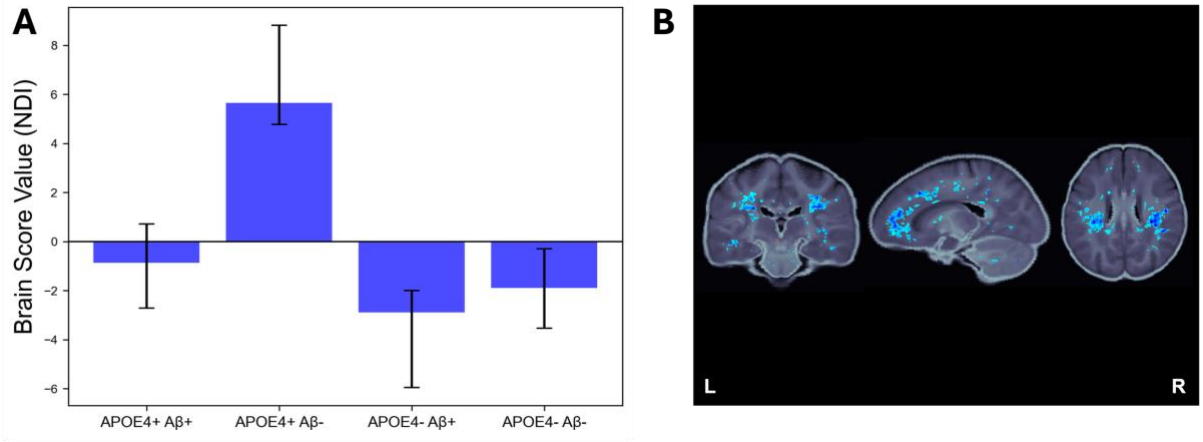

Figure 2.5. A significant association was observed between the Neurite Density Index (NDI) and APOE4-Aβ status that differentiated the APOE4+ Aβ- group from the APOE4- Aβ+ and APOE4- Aβ- groups (panel A). This association was observed bilaterally in the superior longitudinal fasciculus, inferior longitudinal fasciculus (not pictured), forceps minor, and left corticospinal tract (panel B). APOE4 carriers with low amyloid accumulation (indexed by PET SUVR) show reduced axonal packing density compared to APOE4 non-carriers regardless of their amyloid status. This association remains significant when accounting for the effects of age, as pictured here in the age-residualized images.

As noted above, the brain score is a composite score representing the extent to which each participant expresses the group LV pattern, in this instance the NDI associations with APOE4-Aβ PET status. Controlling for sex and education, this brain score was not significantly associated with age (pr(124) = -.004, 95% CI [-.19, .17], p = .962). Controlling for age, sex,

education, and time between PET and NODDI scans, the brain score was not significantly associated with tau-PET ($pr(122) = -.04$, 95% CI [-.20, .12], $p = .675$).

ODI was also significantly associated with Aβ-PET and APOE4 status, however, this pattern was no longer significant when accounting for age in the age-residualized analysis (permuted $p > .198$ across all four LV's).

Discussion

In Study 1, I examined associations between white matter microstructure in preclinical AD and established markers of disease risk. Several key findings emerged. First, as predicted, age was associated with whole-brain white matter microstructural integrity. Specifically, older age was characterized by widespread differences in axonal packing density (NDI), orientation dispersion (ODI), and free water (ISOVF). Second, AD risk markers were most robustly associated with axonal packing density, indexed by NDI. These associations remained significant even when accounting for age, suggesting that the impact of these pathological factors on axonal packing density is observable over and above normal age-related change. Specifically, NDI was lower in the presence of lower circulating levels of Aβ42 (a marker of amyloidosis). This suggests that axonal packing density may be disrupted by amyloid deposits at the very earliest disease stages. In contrast to Aβ markers, NODDI metrics were not associated with tau biomarkers (CSF- or PET-derived). Finally, genetic risk, as determined by APOE4 status, was not directly associated with any NODDI measure. However, a robust inverse association was observed between APOE4 carriers who were Aβ negative and axonal packing density.

Normal Aging Is Associated With Altered White Matter Microstructure

Factors associated with aging can damage postmitotic cells—those that no longer divide or proliferate after differentiation, such as neurons (Frautschy & Cole, 2010; Mattson, 2006).

Axons, being the longest and most morphologically intricate components of neurons (Peng et al., 2021; Wang et al., 2022; Winnubst et al., 2019), are especially susceptible to age-related damage (Groh et al., 2021; Salvadores et al., 2017). These harmful age-related effects are believed to play a crucial role in the development and progression of AD (Frautschy & Cole, 2010; Mattson, 2006). In line with this, Study 1 showed that age was associated with all three NODDI metrics, suggesting broad variations in white matter morphology with aging. NDI exhibited reductions with advancing age (Beck et al., 2021; Cox et al., 2016; Gozdas et al., 2021; Merluzzi et al., 2016; Raghavan et al., 2021) that were noted in limbic and association tracts, as well as projection and commissural fibres. These findings build on the DTI literature and more recent NODDI findings, which have demonstrated that early white matter changes that appear prior to grey matter atrophy or clinical symptoms, are notable in limbic tracts (Motovylyak et al., 2022; Pichet Binette et al., 2021; Wearn et al., 2024; Yin et al., 2015) and shortly thereafter association tracts (Teipel et al., 2016), but also suggest that global axonal packing density is a marker of white matter alterations that accompany aging in at-risk adults, given my observation of more broad reductions that extended to commissural and projection fibres. My results also provide evidence that regions with higher axonal packing density and consequently, greater metabolic activity, are particularly vulnerable to age-related decline (Raghavan et al., 2021; Yang et al., 2023).

A complementary finding to the age-related NDI reductions observed here was an observed pattern of higher ISOVF, suggestive of age-related increases in extracellular free water and sparser tissue structure. Histological evidence indicates that age-related increases in free water correspond to an expansion of the interstitial space, the region between blood vessels and cells (Meier-Ruge et al., 1992). As tissue atrophies with age, these enlarged spaces may allow

water to diffuse more freely. In regions with greater white matter degeneration, reduced axonal packing density may further facilitate unrestricted water movement (Chad et al., 2018). In our sample, the most notable increases in free water were observed in tracts proximal to periventricular regions, particularly the association tracts. In typical aging, periventricular increases in free water have been linked to neurodegenerative processes and attributed to disrupted fluid homeostasis due to ependymal dysfunction, ventricular expansion, impaired CSF flow, and neuroinflammation (Ma et al., 2023; Todd et al., 2018). In AD, dilation of perivascular space and impaired interstitial fluid drainage have been associated with Aβ deposition (Brun & Englund, 1986). However, I did not observe ISOVF associations with PET or CSF markers of amyloidosis in our sample, suggesting that these associations may emerge later in the disease progression.

ODI has been a more difficult metric to interpret as it cannot be directly linked to an underlying neurobiological process (see Chapter 1). Variations in ODI can represent different underlying biological processes depending on the organization of axons within a specific region. Consistent with this idea, here I observed both age-related increases and decreases in ODI. Increases were observed in the forceps minor, while decreases were noted in corticospinal tracts, the inferior fronto-occipital fasciculi, and the anterior thalamic radiations. In other words, whether axons were characterized by decreased or increased orientation dispersion with advancing age, was region-specific. Past studies have noted this pattern and observed that ODI directionality is dependent on the tract tortuosity (i.e., how much a white matter fibre tract deviates from a straight line) and the presence of crossing fibres (Gozdas et al., 2021; Guerreri et al., 2019; Raghavan et al., 2021; Wearn et al., 2024). The age-related increases in ODI observed in the forceps minor—a white matter bundle known for its organized and less complex fibre

arrangement—likely indicate a greater degree of loosening, fanning, and potential bending of the normally aligned axonal bundles with advancing age (Cox et al., 2016; Kodiweera et al., 2016). In contrast, ODI decreases observed in more intricate tracts, such as the anterior thalamic radiations and the inferior fronto-occipital fasciculi, likely reflect a reduction in the structural complexity of the fibres. The corticospinal tract is known to have many crossing fibres, and negative ODI associations with age have been previously documented (Gozdas et al., 2021), consistent with the selective loss of these crossing fibres (Colgan et al., 2016; Fu et al., 2020; Slattery et al., 2017). These findings suggest that increased age is accompanied by a breakdown in the uniform architecture of well-aligned tracts as well as the loss of fibres in more complex or crossing white matter pathways. My findings demonstrate that ODI is able to index these tract-specific changes, suggesting that ODI may be a sensitive marker of early AD-related changes to specific white matter tracts with selective vulnerability to various stages of disease (e.g., Wearn et al., 2024).

Altered White Matter Microstructure Is Associated With AD-Related Neuropathology

Among established neuropathological biomarkers of AD and AD-risk, CSF Aβ42 is one of the first to show abnormalities linked to underlying pathophysiological processes (Jack et al., 2013; Zetterberg & Bendlin, 2021). Among NODDI metrics, NDI is the most sensitive to CSF amyloidosis markers in cognitively unimpaired older adults (Moody et al., 2022). My findings build on this work by demonstrating associations between NDI and CSF Aβ42 in cognitively unimpaired individuals with known risk for AD, while controlling for age. As such, NDI may provide early evidence for amyloid-related changes at the earliest stages of disease, potentially circumventing the need for more invasive detection methods such as PET or lumbar punctures.

Interestingly, while NODDI associations were observed with CSF Aβ42, these associations were not directly observed with PET-derived markers of Aβ. One explanation could be differences in variable quantification. To allow for group comparisons, Aβ-PET status was derived as a categorical variable, while CSF-Aβ42 was treated as continuous, which supported a potentially more sensitive analysis of its association with NODDI metrics. However, the temporal difference between CSF and PET biomarkers is well established (Jack et al., 2013; Zetterberg & Bendlin, 2021), with about 20% of individuals at preclinical stages of AD demonstrating divergence in these markers (Mattsson et al., 2015). Divergent Aβ results are regularly observed regardless of cutoffs used, even when intentionally created to maximize concordance (Sala et al., 2021). A recent cross-sectional and longitudinal study found that CSF and Aβ-PET biomarkers offer distinct insights into brain Aβ burden and accumulation rates. Indeed, divergence between these biomarkers strongly predicts progression toward full Aβ pathology (Sala et al., 2021). Specifically, the authors discovered two discordant pathways to Aβ pathology: a "CSF-first" trajectory and a "PET-first" trajectory. Individuals in the "CSF-first" group (CSF+/PET−) exhibited faster amyloid accumulation in the brain, and eventually become Aβ-PET+, possibly reflecting the rate at which soluble Aβ is deposited into insoluble plaques. Interestingly, this group had a higher proportion of APOE carriers with two copies of the ε4 allele. In contrast, the "PET-first" group (CSF−/PET+) accumulated amyloid more slowly, with only 30% of individuals progressing to CSF Aβ+. Given this, the lack of NODDI associations with Aβ-PET in this dissertation could reflect both methodological differences as well as the inherent temporal and biological discrepancies between CSF and PET amyloid measures expected at early disease stages.

While significant relationships between NDI and the CSF p-tau/Aβ42 ratio have been reported (Moody et al., 2022), I failed to replicate this finding. This discrepancy may be attributable to differences in the constitution of the study cohorts, including sample size and disease staging, or methodological differences in deriving CSF markers. However, further research will be necessary to confirm the specific nature of these associations.

Genetic Risk for AD Is Indirectly Associated with Altered White Matter Microstructure

I examined white matter microstructural associations with the APOE4 genotype. APOE4 is the most significant genetic risk factor for sporadic AD, due to its involvement in myelin regulation (Blanchard et al., 2022). Contrary to my predictions, I did not find any group differences between APOE4 carriers and non-carriers. Epidemiological studies of preclinical cohorts have demonstrated an association between Aβ pathology and APOE genotypes (Jansen et al., 2022; Jansen et al., 2015). As such, I conducted a follow-up analysis examining APOE4 status stratified by Aβ-PET status. This secondary analysis revealed an interesting interaction between genetic risk and APOE status such that lower white matter integrity (NDI) was only observed in the APOE4+ Aβ- group, distinguishing this cohort from both the APOE4- Aβ- and APOE4- Aβ+ groups. These results show that white matter density reductions at preclinical stages are specific to APOE4 carriers with below-threshold Aβ, compared to APOE4 non-carriers, regardless of non-carrier amyloid status.

This is one of the first investigations of APOE4 associations with white matter microstructure using NODDI metrics in preclinical AD. Earlier findings using DTI techniques have shown poor agreement regarding the extent of white matter abnormalities in APOE4 carriers in typical aging, with studies reporting changes in diffusion metrics (Lopez et al., 2003; Petersen et al., 2014; Ungar et al., 2014), null findings (Kryscio et al., 2006; Tervo et al., 2004),

or inconsistent results (Boyle et al., 2010). While APOE4 increases disease risk, APOE2 carriers have a lower disease risk, with evidence suggesting greater protection for women than men (Neu et al., 2017). Recently, these findings have been extended to investigations of white matter alterations, noting that the antagonistic impacts of APOE2 and APOE4 on brain microstructure are observed only in women (Reas et al., 2024). This interaction between APOE genotype, sex, and Aβ status may contribute to the nuances observed in my results. In this study, I did not explore sex differences given our predominantly female sample. I also did not investigate APOE2 effects due to limited power. Specifically, our sample included only 5 participants with both APOE4 and APOE2 (3 of whom were PET-Aβ+), and 15 with both APOE3 and APOE2 (3 of whom were PET-Aβ+). These constraints limited my ability to further investigate potential associations between sex, APOE genotype, and white matter microstructure.

To my knowledge, this is the first investigation of interactions between genetic risk and the presence of AD-related neuropathology, and impact on white matter microstructure. My finding that APOE status indirectly impacts white matter *in the absence of Aβ deposition* was unexpected. Given that persons with the APOE4 allele but without significant Aβ deposition represent the most exceptional cohort in this analysis, the finding raises intriguing questions as to other potential neuropathological mechanisms of white matter degradation linked to APOE4 status, including tauopathies.

Tauopathy Was Not Associated With Altered White Matter Microstructure

Tau-PET studies indicate that early stages of AD (preclinical to MCI) show tau-related white matter degeneration characterized by decreased NDI (Wen et al., 2021). A more recent study has demonstrated that preclinical participants from the same cohort studied in this dissertation who had higher CSF p-tau concentrations more strongly express a negative

covariance pattern between NDI and ODI, which is more evident in APOE4 carriers, suggesting its specificity for AD (Wearn et al., 2024). However, in this study, I did not identify any significant relationships between NODDI metrics and biomarkers of tau, including CSF and PET measurements. While non-significant, the pattern of tau-PET deposition in association with NDI, showed striking spatial overlap with the NDI and age covariance pattern. Indeed, in my preliminary data analyses, a positive correlation was identified between age and tau-PET. Tau pathology is found in normal aging, even in the absence of Aβ (Bouras et al., 1994; Braak et al., 2011). This phenomenon has been referred to as primary age-related tauopathy (PART; Crary et al., 2014; Jellinger et al., 2015), although PART has also been suggested to be part of the AD spectrum (Duyckaerts et al., 2015). Empirical evidence supports the possibility of two distinct trajectories for tau pathology in aging. The first path is characterized by medial temporal lobe tau pathology attributable to chronological age, while the second path links cortical tau pathology (i.e., lateral and inferior temporal and other neocortical regions) to interactions with cortical Aβ pathology (Price & Morris, 1999; Small & Duff, 2008). In my study, correlations between tau and Aβ pathology biomarkers were not observed, although all tau measures (CSF p-tau, t-tau, and tau-PET) exhibited correlations with one another. Furthermore, there were no significant associations identified between tau-PET pathology and NDI, ODI, or ISOVF when comparing Aβ-PET positive and negative individuals. Instead, all identified alterations in white matter microstructure appeared to be more closely related to Aβ pathology. It has been noted that abnormal Aβ biomarkers are a prerequisite for neocortical AD tauopathy (Jack Jr et al., 2019), suggesting that the current findings may reflect changes in white matter microstructure that occur before the impacts attributable to tauopathies emerge. Alternatively, the characterization of tau-PET pathology adopted here, while standard in the literature, combines medial temporal and

cortical regions, potentially obscuring region-specific associations between the presence of tau and alterations in white matter microstructure.

Conclusion

In summary, the results of Study 1 suggest that in cognitively unimpaired older adults at elevated risk for AD, advancing age is accompanied by broad alterations in white matter morphology, including reduced axonal packing density, disruption of tract organization, and increased extracellular free water associated with sparser tissue structure. Furthermore, interactions between Aβ pathology and genetic risk are related to altered white matter microstructure at preclinical stages. Among the NODDI metrics, NDI appears to be the most sensitive to associations with markers of disease risk at the preclinical stage of disease. This suggests that reductions in axonal packing density are amongst the earliest microstructural signs of underlying AD-related disease pathology in white matter.

CHAPTER 3

Study 2: White Matter Microstructure and Cognition in Preclinical Alzheimer's Disease

White matter pathways facilitate communication between spatially separate grey matter regions. In doing so, they support cognitive processes (Fields, 2008; Filley & Fields, 2016). Not surprisingly, AD-related changes in white matter microstructure have been strongly associated with cognitive impairments that gradually manifest as AD progresses (Bozzali et al., 2002; Huang et al., 2007; Scheltens et al., 1995; Takahashi et al., 2002; Zhuang et al., 2013). Over the past two decades, studies linking white matter structure to cognitive aging using DTI methods have identified ***episodic memory*** (Bennett & Madden, 2014; Coelho et al., 2021; Fjell et al., 2016; Kennedy & Raz, 2009; Lockhart et al., 2012; Ly et al., 2016; Persson, Nyberg, et al., 2006; Rabin et al., 2019; Ryan et al., 2011; Voineskos et al., 2012; Ziegler et al., 2010), ***executive control*** (Brickman et al., 2012; Chung et al., 2020; Coelho et al., 2021; Cremers et al., 2016; Fjell et al., 2017; Grieve et al., 2007; Hedden et al., 2016; O'Sullivan et al., 2001; Perry et al., 2009; Ryan et al., 2011; Zahr et al., 2009), and ***processing speed*** (Cremers et al., 2016; Hedden et al., 2016; Kennedy & Raz, 2009; Kerchner et al., 2012; Kuznetsova et al., 2016; Laukka et al., 2013; Lövdén et al., 2014; Penke et al., 2010; Rabin et al., 2019; Salami et al., 2012) as among the most impacted cognitive domains with respect to declines in white matter integrity. However, there is considerable variability across studies, likely attributable to the myriad cognitive domains examined, neuropsychological measurement, and study designs (cross-sectional vs. longitudinal).

More recent studies examining NODDI metrics of white matter microstructure suggest that these measures may be more sensitive than traditional DTI techniques (Raghavan et al., 2021; Wen et al., 2019) for mapping white matter structure to cognitive status and AD staging

(Fu et al., 2020; Tian et al., 2023). NDI has shown robust associations with screeners of global cognitive performance (Tian et al., 2023), as well as with memory (Gozdas et al., 2021), attention, language, visuospatial abilities (Raghavan et al., 2021), and executive abilities (Motovylyak et al., 2022) across the AD spectrum. Compared to NDI, ODI generally shows weaker or absent correlations with cognitive performance (Gozdas et al., 2021; Motovylyak et al., 2022; Raghavan et al., 2021). Despite this, ODI has been linked to performance on measures of episodic memory and cognitive screeners in samples across all stages of disease (Fu et al., 2020; Wen et al., 2019). Similarly, ISOVF has demonstrated significant associations with measures of general cognitive status (Fu et al., 2020) and is a reliable predictor of slower processing speed as well as global cognitive decline (Raghavan et al., 2021). However, unlike NDI and ODI, ISOVF has not been associated with episodic memory (Gozdas et al., 2021; Motovylyak et al., 2022; Raghavan et al., 2021). While in some cases ODI and ISOVF have outperformed DTI (Fu et al., 2020), NDI emerges as a more robust and reliable predictor of cognitive decline across the AD spectrum.

While NODDI is becoming a prominent technique for identifying white matter changes in clinical stages of AD, its efficacy in the earliest stages of disease, before emergence of the clinical syndrome has yet to be comprehensively examined. Additionally, the connection between early axonal structural alterations and cognitive outcomes remains unclear. In one study examining four white matter tracts in cognitively unimpaired individuals with a parental history of AD, NDI showed positive associations with executive control. While no other NODDI metrics were linked to cognition, it is worth noting that the study did not assess processing speed as a separate cognitive domain but included a processing speed-dominant measure (Digit Symbol Coding) within the executive control composite score (Motovylyak et al., 2022). This is

important given that processing speed has been demonstrated to be closely linked to white matter integrity (Baykara et al., 2016; Konieczny et al., 2021; Raghavan et al., 2021). In another sample enriched for AD risk (72% with parental history), NDI predicted poorer performance on verbal list learning and letter-number sequencing tasks. However, this study limited their evaluations to these two cognitive tests and restricted their cognitive analyses to frontal white matter (Merluzzi et al., 2016). While this area of inquiry is still nascent, examinations of white matter microstructure using NODDI metrics as predictors of cognition have yet to comprehensively examine whole brain white matter microstructure and multidomain cognition.

In typical aging, there is uncertainty regarding whether cognitive changes stem from changes in specific white matter tracts or from widespread alterations across the entire brain (Bennett & Madden, 2014). While the cross-sectional evidence is mixed, longitudinal investigations suggest a global effect (Coelho et al., 2021; Rabin et al., 2019). This is further supported by studies demonstrating that integrity within white matter tracts is highly correlated (Cox et al., 2016; Gozdas et al., 2021; Lövdén et al., 2014; Penke et al., 2010). While AD-related changes may be tract-specific (Gold et al., 2012; Teipel et al., 2014; Wu et al., 2010; Zhang et al., 2011; Zhuang et al., 2013), widespread alterations in white matter have been previously associated with cognitive decline (Mayo et al., 2019). Given preclinical AD represents a critical transition phase from typical aging to atypical aging, occurring before noticeable cognitive symptoms emerge, it remains unclear whether white matter changes during this period reflect the more diffuse alterations seen in normal aging or the tract-specific changes associated with the symptomatic stages of AD.

Given this, the aim of the second study was to examine white matter microstructure associations with cognition in preclinical AD using a whole-brain exploratory approach. In

particular, the goal was to examine how preclinical morphological variations in white matter microstructure are related to the three cognitive domains most consistently identified in the DTI-literature: episodic memory, processing speed, and executive control. Analyses were conducted on the same sample as in Study 1; a cohort of cognitively unimpaired older adults with familial AD risk based on first-degree relatives. In Study 2, I applied a data-driven multivariate analytical model to examine each NODDI metric (NDI, ODI, and ISOVF) in association with an index score for each cognitive domain of interest (episodic memory, processing speed, and executive control). I hypothesized that in preclinical AD: (1) NODDI metrics would be associated with cognition in each of these domains; (2) NDI would show the most robust associations across domains; (3) episodic memory would show the most robust associations with white matter microstructural integrity given the selective vulnerability of declarative memory to AD-related neuropathology.

Method

The methods for Study 2, including participant demographics, data collection, neuroimaging protocol and acquisition, and NODDI processing, are identical to those reported in Study 1. They are replicated here for the reader's convenience.

Participants

Data were drawn from the Preclinical EValuation of Experimental or Novel Treatments for AD (PREVENT-AD) cohort (Tremblay-Mercier et al., 2021). All data have been de-identified and are available for open access. All study participants provided informed written consent prior to study participation. The procedures of the PREVENT-AD study were administered in compliance with the McGill institutional review board and/or the Douglas Mental Health University Institute Research Ethics Board. Additional approval for the current

dissertation was provided by the institutional review board at York University. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. To increase the probability that participants would exhibit the earliest changes associated with asymptomatic AD, entry criteria into the PREVENT-AD cohort required intact cognition and a parental or multiple-sibling family history of AD. The cohort underwent genotyping and was tracked through naturalistic studies assessing cognition, neurosensory capacities (i.e., smell identification and auditory processing), CSF biochemistry, MRI, and medical and clinical evaluations. Of the 146 participants from Study 1, 138 participants had a complete cognitive dataset.

Neuroimaging Protocol

Methods related to neuroimaging protocol, acquisition, and processing have been previously published (Wearn et al., 2024) and are reviewed here. Neuroimaging data were collected using a 3T Siemens PrismaFit MRI scanner at the Douglas Research Centre. All participants underwent T1-weighted imaging and multi-shell diffusion MRI. T1-weighted anatomical scans were acquired using a 3-dimensional magnetization rapid gradient echo (MPRAGE) sequence (1mm isotropic resolution, TR/TE/TI = 2300/2.96/900ms, FA = 9°, TA = 5:30). Multi-shell diffusion-weighted imaging employed a 2mm isotropic spin-echo echo-planar imaging sequence. A total of 109 diffusion-weighted directions were sampled, evenly distributed across three shells with the following diffusion weightings: 7 directions at b=300 s/mm², 29 at b=1000 s/mm², and 64 at b=2000 s/mm². Additionally, 9 b=0 images were acquired using a TR/TE of 3000/66 ms and posterior-to-anterior phase encoding. For distortion correction, an extra set of five b=0 images were collected using the same sequence parameters but with reversed phase encoding (anterior-to-posterior). The complete acquisition time for the sequence

was 5 minutes and 49 seconds. All imaging sequences provided complete coverage of the brain and encompassed the brainstem.

Neurite Orientation Dispersion and Density Imaging

Neurite orientation dispersion and density imaging (NODDI) was used to assess white matter microstructure (Zhang et al., 2012). NODDI relies on multi-shell diffusion encoding and a multi-compartment biophysical model of brain tissue which enables it to provide more specific and clinically meaningful parameters.

NODDI Processing

MRtrix3 toolbox was used to preprocess all diffusion data (Tournier et al., 2019). Preprocessing steps included denoising (*dwidenoise*) (Cordero-Grande et al., 2019; Veraart, Fieremans, et al., 2016; Veraart, Novikov, et al., 2016), as well as correction for eddy current distortion, susceptibility artifacts, and motion artifacts (*dwifslpreproc*) (Andersson et al., 2003; Andersson & Sotiropoulos, 2016; Smith et al., 2004). Images were upsampled to 1mm isotropic resolution (*mrgrid*) and then underwent brain extraction (bet2) (Smith, 2002) and bias-field artifact correction with the ANTs algorithm (N4) (Tustison et al., 2010) of the *dwibiascorrect* MRtrix function. The NODDI model was fitted to the bias field corrected diffusion-weighted data using the Accelerated Microstructure Imaging via Convex Optimization (AMICO) implementation in Python (Daducci et al., 2015; Zhang et al., 2012). Response functions were calculated for each compartment. Model fitting was subsequently applied to the bias-corrected diffusion-weighted volumes restricted to the brain mask. The derived metrics include the neurite density index (NDI), the isotropic volume fraction (ISOVF), and the orientation dispersion index (ODI). NODDI metrics were examined across the whole brain white matter. The *5ttgen* function

of MRtrix3 was used to develop a probabilistic mask of normal-appearing white matter for each participant (Smith et al., 2012).

Normalization of NODDI Map to MNI Space. Upsampled NODDI maps, along with probabilistic white-matter masks, were aligned to MPM maps using FSL's 'flirt' tool. This was done through rigid-body registration, where b=0 diffusion-weighted images served as the moving image and proton density (PD) maps were used as the reference due to their similar contrast properties. Next, MTsat maps were segmented into different tissue classes (i.e., grey matter and white matter). Deformation fields were then computed to convert the native brain space to the standardized MNI (2009c) space using the 'Shoot' toolbox in SPM12 (Ashburner & Friston, 2011). These deformation fields were subsequently used to transform the NODDI maps and white-matter masks into MNI template space. The MNI-warped white-matter masks were averaged across participants and thresholded at 0.95 to retain only regions with a 95% probability of being white matter. Images were then smoothed using a 1mm full-width half-maximum Gaussian kernel to enhance image quality. The derived images were used for partial least squares (PLS) analysis (described below).

Age Regressed Residual Images. A second set of NODDI data accounting for age was created to supplement each original NODDI map. This age-residualized dataset was developed to control for potential age-related variability in white matter metrics, given that age has been shown to have strong associations with white matter changes. This approach allows for a clearer examination of the specific relationships between NODDI measures and cognition without the confounding influence of age. Multiple regression was used to regress age from the unsmoothed NODDI maps described above, implemented in SPM12. Age residualized images were subsequently smoothed with a 1mm full-width half-maximum Gaussian kernel. The resulting

residual images were inputted into the partial least squares (PLS) analysis, where appropriate (described below).

Behavioural Assessment of Neurocognitive Functioning

Performance on standardized measures of episodic memory, processing speed, and executive control was assessed to characterize cognitive abilities of each participant. Episodic memory was examined with the Rey Auditory Verbal Learning Test (RAVLT) Immediate Recall (totals for trials 1–5) and Delayed Recall trials (Schmidt, 1996). Processing speed was assessed with the Delis-Kaplan Executive Function System (DKEFS) Colour-Word Interference (Colour Naming time and Word Reading time) (Delis et al., 2001), and Trail Making Test (TMT) A Time (Reitan, 1985; Tombaugh, 2004). Executive control was examined with TMT Trails B – Complex Alternating Attention Score (TMT B time minus TMT A time) (Reitan, 1985; Tombaugh, 2004), DKEFS Colour-Word Interference (Inhibition Time and Inhibition/Switching Time) (Delis et al., 2001).

Raw participant data on each individual test measure were converted to a z-score [$z = (\text{raw score}-\mu)/\sigma$]. Then, to derive a domain-specific index score for each participant, z-scores for each test measure were averaged. This resulted in three index scores for each participant: Episodic Memory Index, Processing Speed Index, and Executive Control Index. For the Episodic Memory Index, higher scores are indicative of better performance. For the Processing Speed and Executive Control Indices, lower scores are indicative of better performance (i.e., faster performance). Theoretically derived domain-specific index (also known as composite) scores have been demonstrated as more appropriate for cognitively unimpaired samples and have shown lower intraindividual variability over time and stronger age interactions with Aβ compared to empirically derived indices (e.g., using factor analysis) or scores from single tests (Jonaitis et al.,

2019). Implementation of index scores instead of individual test scores also minimizes measurement error and the likelihood of Type I error due to multiple comparisons, thereby maximizing statistical power.

Statistical Analysis

As in Study 1, a preliminary analysis was conducted to examine associations between demographic and behavioural variables in this sample. Pearson correlation based on 1000 bootstrapped samples was calculated to assess the associations between age, education, the Episodic Memory Index, the Processing Speed Index, and the Executive Control Index. Two extreme scores were identified in the Executive Control Index in these analyses. The Executive Control Index was subsequently recalculated without these participants (n = 136), and the resulting adjusted index scores were used in all analyses that followed.

bPLS was performed to identify associations between NODDI metrics (NDI, ODI, ISOVF) and cognition (Episodic Memory Index, Processing Speed Index, and Executive Control Index) (McIntosh & Lobaugh, 2004; McIntosh & Mišić, 2013). The reader is referred to Study 1 for a more in-depth description of bPLS and parameters used for the analyses. In Study 2, cognitive indices were treated as behavioural variables and each PLS analysis examined the relationship between one NODDI metric and one cognitive index at a time. Permutation tests of 1000 samples were used to evaluate the significance of the brain-wide data of each NODDI metric associated with each cognitive index captured by a given latent variable (LV), while 1000 bootstrap samples were used to determine its reliability. Significant PLS associations between the original NODDI map and cognition were re-analyzed a second time with the age-residualized maps to examine these patterns when the effects of age are accounted for.

As in Study 1, the JHU white-matter tractography atlas (Hua et al., 2008) was used to assist with visual identification of white matter pathways for each statistically significant pattern identified by PLS. For enhanced visualization, all brain images were more stringently thresholded to ±2.57 (approximately $p < 0.01$), unless stated otherwise.

Results

Prior to testing Study 2 hypotheses, the relationships between all behavioural variables in this sample were examined. Pearson correlations with CI's based on 1000 bootstrapped samples were calculated to assess the associations between age, education, and cognitive indices. P-values were Bonferroni corrected for multiple comparisons (shown as p_{adj}). The analysis identified a negative relationship between age and the Episodic Memory Index ($r(136) = -.25$, $p_{adj} < .001$, 95% CI [-.41, -.09]) and a positive relationship with the Executive Control Index ($r(136) = .28$, $p_{adj} < .001$, 95% CI [.12, .41]), the latter which remained significant after removing two extreme scores from the sample ($r(134) = .25$, $p = .001$, 95% CI [.08, .40]). A negative relationship was observed between education and the Executive Control Index ($r(136) = -.21$, $p_{adj} = .03$, 95% CI [-.34, -.05]), which remained significant after removing two extreme scores ($r(134) = -.19$, $p = .015$, 95% CI [-.36, -.02]). A negative relationship was also identified between the Executive Control and Episodic Memory Indices $r(136) = -.20$, $p_{adj} = .04$, 95% CI [-.40, -.02]), which remained significant even when the extreme scores from the sample ($r(134) = -.26$, $p = .001$, 95% CI [-.44, -.07]). Finally, a moderate positive association was observed between the Executive Control and Processing Speed Indices ($r(136) = .43$, $p_{adj} < .001$, 95% CI [.25, .60]). This finding remained significant even when removing two extreme scores from the sample ($r(134) = .46$, $p < .001$, 95% CI [.27, .61]). No other significant correlations were noted between covariates (see Tables 3.1 for a summary of all results).

Table 3.1
Pearson Correlation Matrix of Cognition and Demographics (n=138)

	Education	Age	Episodic Memory Index	Processing Speed Index	Executive Control Index
Education	-				
Age	.03 [-.16, .20]	-			
Episodic Memory Index	.09 [-.06, .22]	-.25** [-.41, -.09]	-		
Processing Speed Index	-.09 [-.23, .04]	.15 [-.03, .31]	-.05 [-.24, .16]	-	
Executive Control Index	-.21* [-.34, -.05]	.28** [.12, .41]	-.20* [-.40, -.02]	.43** [.25, .60]	-

Note. Values in square brackets indicate the 95% confidence interval for each correlation. CI's are based on 1000 bootstrap samples. *p < .05; **p < .01

To investigate how white matter microstructure in preclinical AD relates to cognition, bPLS was used to determine multivariate associations between the previously calculated NODDI metrics and indices of episodic memory, processing speed, and executive control.

White Matter Microstructure and Episodic Memory

As predicted, a significant association was observed between NDI and the Episodic Memory Index (r = .32, 95% CI [.19, .46], permuted p = .008), suggesting that episodic memory declines with decreased axonal packing density (Figure 3.1A). This association was observed bilaterally in the corticospinal tract, superior longitudinal fasciculus, and forceps minor (L>R; not pictured). When accounting for the effects of age in the age-residualized analysis, this finding approached significance (r = .31, 95% CI [.08, .53], permuted p = .073; Figure 3.1B). See Appendix C for original non-age residualized figure and Appendix I for MNI coordinates.

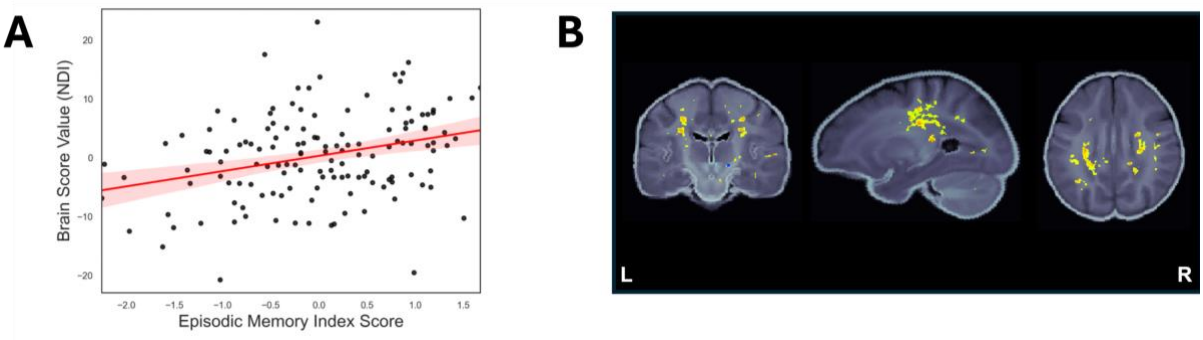

Figure 3.1. A significant association was observed between the Neurite Density Index (NDI) and the Episodic Memory Index (panel A). This association was observed bilaterally in the corticospinal tract, superior longitudinal fasciculus, and forceps minor (L>R; not pictured) (panel B). Axonal packing density reductions are associated with declines in episodic memory performance. This association approaches significance (p = .073) when accounting for the effects of age in the age-residualized analysis, as pictured here (bottom panel).

A significant association was also observed between ODI and the Episodic Memory Index (r = .61, 95% CI [.52, .71], permuted p = .002; Figure 3.2A). Specifically, a decline in episodic memory was associated with ODI decreases in the forceps minor on the right (not pictured) and corticospinal tracts bilaterally, as well as bilateral ODI increases in the inferior fronto-occipital fasciculus and cerebellum (Figure 3.2B; see Appendix J for MNI coordinates), providing evidence that associations between neurite dispersion and episodic memory are tract specific. While this relationship was not statistically significant when controlling for age (r = .69, 95% CI [.60, .79], permuted p = .109), the robustness of the effect, as well as evidence for tract specificity, suggests that ODI may be an informative marker of altered white matter microstructure in the earliest stages of AD.

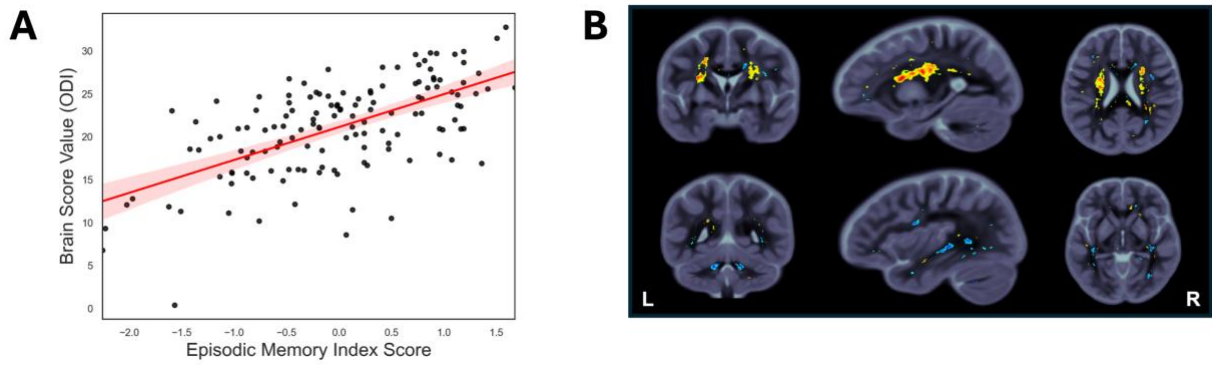

Figure 3.2. A significant association was observed between the Episodic Memory Index and the Orientation Dispersion Index (ODI) (panel A). A decline in episodic memory is associated with axonal orientation dispersion decreases in the forceps minor on the right (not pictured), and the corticospinal tract bilaterally (warm colours; panel A) as well as bilateral increases in the inferior fronto-occipital fasciculus and cerebellum (cool colours; panel B). This association was not significant when accounting for the effects of age in the age-residualized analysis.

No significant associations were observed between ISOVF and the Episodic Memory Index (r = .83, 95% CI [.76, .89], permuted p = .114).

White Matter Microstructure and Processing Speed

No significant associations were observed between the Processing Speed Index and any of the NODDI metrics (all permuted p's > .25).

White Matter Microstructure and Executive Control

PLS identified a significant association between ODI and the Executive Control Index (r = .67, 95% CI [.58, .77], permuted p = .049; Figure 3.3A). Higher Executive Control Index scores (poorer performance) were predominantly associated with ODI reductions bilaterally in the corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus (not pictured), and cerebellum (blue regions), as well as increased bilateral dispersion around the brainstem and a tract superior to the forceps minor and cingulum in the left hemisphere that could not be visually identified with the JHU atlas (yellow regions) (Figure 3.3B; See Appendix K for MNI coordinates). As such, worse executive functioning was associated with axonal orientation

dispersion increases and decreases. These results did not remain significant after controlling for age in the age-residualized analysis (r = .87, 95% CI [.78, .90], permuted p = .91). However, these results again suggest ODI's sensitivity to altered white matter microstructure in the earliest stages of AD, given the robustness of the effect and evidence for tract specificity.

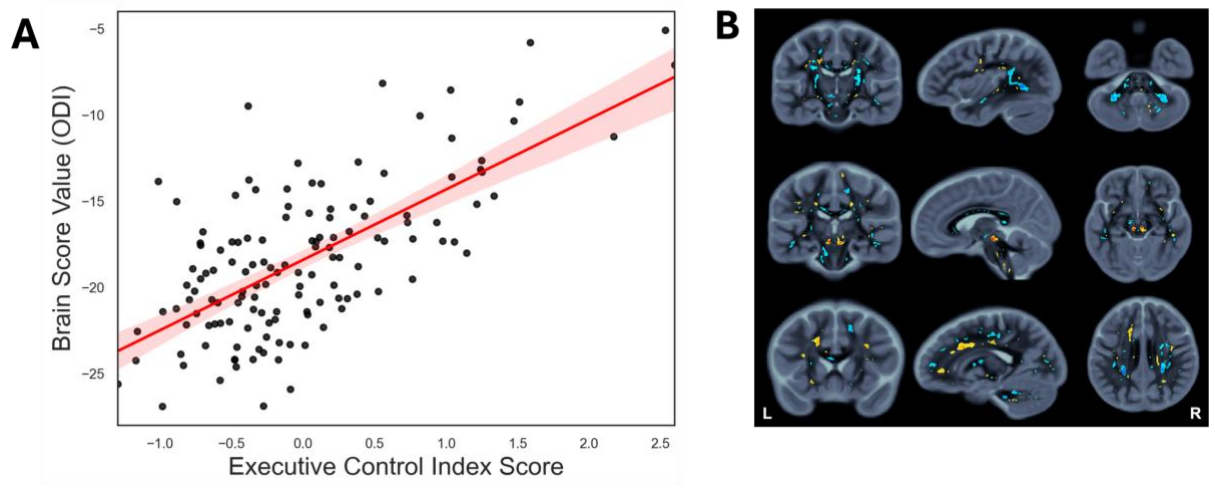

Figure 3.3. A significant association was observed between the Executive Control Index and the Orientation Dispersion Index (ODI) (panel A). A decline in executive control is associated with axonal orientation dispersion decreases bilaterally in the corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus (not pictured), and cerebellum (cool colours; panel B, top row). Bilateral ODI increases were observed around the brainstem (panel B, middle row) as well as a tract in the left hemisphere superior to the forceps minor and cingulum (panel B, bottom row) that could not be identified with the JHU atlas (warm colours). For enhanced visualization, the brain images were thresholded to ±1.98 (approximately $p <$ 0.05). This association did not remain significant when accounting for age effects in the age-residualized analysis.

A significant association was also observed between ISOVF and the Executive Control Index (r = .80, 95% CI [.78, .89], permuted p = .006; Figure 3.4A). Higher Executive Control Index scores (poorer performance) were associated with increased free water in the left forceps major, superior longitudinal fasciculus bilaterally, and left cingulum bundle (warm colours) as well as decreases in the brainstem (cool colours) (Figure 3.4B; see Appendix L for MNI coordinates). As with ODI, the Executive Control-ISOVF association did not remain significant

after controlling for the effects of age in the age-residualized analysis (r = .87, 95% CI [.79, .92], permuted p = .16).

NDI was not found to be significantly associated with the Executive Control Index (r = .29, 95% CI [-.02, .60], permuted p = .299).

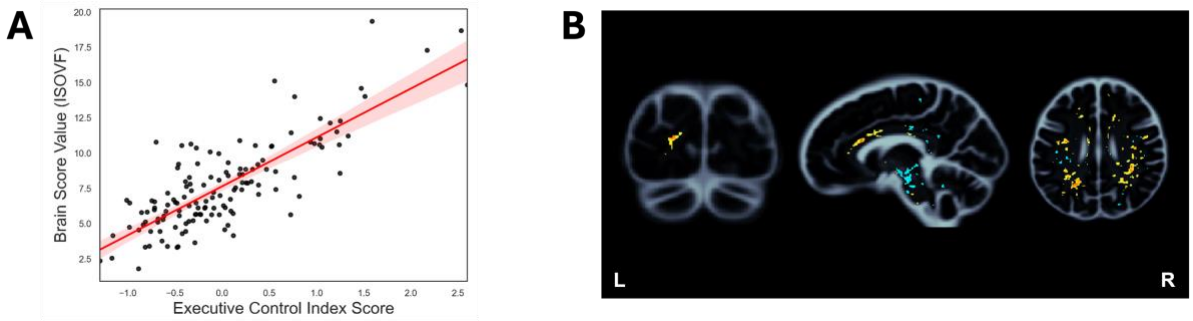

Figure 3.4. A significant association was observed between the Executive Control Index and free water (ISOVF) (panel A). A decline in executive control is associated is associated with increased free water in the left forceps major, superior longitudinal fasciculus bilaterally, and left cingulum bundle (warm colours) as well as decreases in the brainstem (cool colours). For enhanced visualization, the brain images were thresholded to ±1.98 (approximately $p < 0.05$). This association did not remain significant when accounting for age effects in the age-residualized analysis.

Discussion

In Study 2, associations between white matter microstructure in preclinical AD and cognition were investigated. As predicted, I observed reliable associations between NODDI metrics of white matter integrity and cognitive performance. NDI, a measure of axonal packing density, was the most sensitive metric wherein reliable associations were observed over and above age-related effects. Finally, as predicted, episodic memory was the only cognitive domain to show associations with declining white matter microstructure, when accounting for the effects of age.

Axonal Packing Density Is Related to Episodic Memory Performance

Episodic memory is impacted in both typical and atypical aging (Tromp et al., 2015). Long considered the hallmark of AD-related cognitive change, a decline in episodic memory is a hallmark predictor of the emergence of a clinical syndrome (Binetti et al., 1996; Burnham et al., 2016; Derby et al., 2013; Schindler et al., 2017). Consistent with prior work (Gozdas et al., 2021; Merluzzi et al., 2016), I observed that NDI, an index of axonal packing density, exhibited an association with episodic memory, and this association held after controlling for age, given my *a priori* prediction of a positive association. These findings provide the first evidence for an association between white matter morphology and episodic memory observed in an at-risk, cognitively unimpaired population of older adults, while controlling for the effects of age. These effects were observed across association tracts, projection fibres, as well as interhemispheric callosal fibres, suggesting that global axonal packing density serves as marker of episodic memory performance in this cohort of at-risk older adults. An important next step for future research will be to examine whether tract specific differences in NDI measures may provide more sensitive and specific markers of cognitive function in asymptomatic stages of disease.

On a related point, specific tract-wise associations were observed between ODI and episodic memory performance. This pattern included both dispersion increases in longitudinal association fibre tracts as well as decreases in more tightly bundled projection fibre tracts. As reviewed in Chapter 1, these divergent patterns of ODI change may both be considered markers of declining white matter microstructure given the different morphological architectures of these various tracts. As such, ODI may hold significant promise for detecting tract-specific changes that portend specific patterns of cognitive decline.

Axonal Orientation Dispersion and Free Water Alterations Are Related to Executive Control

Though a positive association was observed between ODI and executive control performance, this effect was not significant after accounting for age. While this finding is consistent with previous studies, reporting weak or absent correlations between ODI and cognition across the AD spectrum (Gozdas et al., 2021; Raghavan et al., 2021), it is important to note that that pattern of brain changes included both increases and decreases in ODI associated with executive control, again hinting at potential tract specificity in these preliminary findings. As observed in the ODI associations with episodic memory, ODI decreases were identified in the corticospinal tracts, though this time, reductions were also observed in long-range association fibers. Interestingly, *increased* axonal dispersion was observed in the brainstem, one of the earliest regions known to be affected by tau pathology in AD (e.g., Al-Shaikh et al., 2020; Beardmore et al., 2021; Fernández-Cabello et al., 2020; Jacobs et al., 2021; Schmitz & Spreng, 2016) and considered to be a neural substrate for AD-related clinical symptoms, including changes in cognition and behaviour (Grinberg et al., 2011; Lee et al., 2015). Indeed, ODI alterations in brainstem tracts have been previously noted in our sample (Wearn et al., 2024). These ODI results in Study 2 were mirrored in the ISOVF analysis, which revealed increases in association fibres and decreases in brainstem tracts associated with poorer executive control—an effect that did not remain significant after accounting for age. While ISOVF increases align with predictions suggesting extracellular free water expansion and sparser tissue structure, the observed ISOVF reductions were unexpected. It may be possible that the free water reductions occur in response to a build-up of misfolded pathological tau proteins, which aggregate in the extracellular space before they are absorbed by nearby cells in a prion-like fashion, a self-

propagating mechanism of disease spread in neurodegenerative disease (Brunello et al., 2020; Jucker & Walker, 2013). Decreased extracellular free water could also be reflective of toxin accumulation by the neuromelanin-containing cells in the locus coeruleus in the brainstem, which can be worsened due to AD-related reduced blood-brain barrier integrity (Kisler et al., 2017; Satoh & Iijima, 2019; see Beardmore et al., 2021; Matchett et al., 2021 for reviews).

Previous work examining white matter microstructure in older adults has reported associations between NDI and executive control in brain regions which show particular vulnerability to age-related decline (Motovylyak et al., 2022). While I did not replicate these earlier findings here, differences may be attributable to how executive control was operationally defined. The earlier work included processing speed within their executive control index whereas I defined a separate index for processing speed here. Integrating both executive control and processing speed, both of which rely on distributed processing and long-range connectivity across brain regions, may have enabled the detection of associations between NDI, a more global measure of white matter integrity and executive control in the earlier study. Moreover this earlier report also included a wider age range, encompassing middle age, further hindering the ability to draw direct comparisons with my work, given the shifting trajectories of NDI change from middle to late adulthood (Chang et al., 2015; Cox et al., 2016).

Other Factors Influencing Associations Between White Matter Microstructure and Cognition

No other significant relationships between NODDI metrics and episodic memory, executive control, or processing speed were observed. While speculative, my null findings when accounting for the effects of age, may reflect more complex, possibly compensatory changes in white matter composition. In cognitively normal older adults, cognitive decline typically occurs

when Aβ levels are high and white matter integrity is compromised. However, when Aβ burden is lower, increases in FA and decreases in MD and RD have been observed and these changes are associated with preserved cognitive function (Wolf et al., 2015) suggesting a putative compensatory mechanism (Molinuevo et al., 2014).

A second potential complicating factor obscuring brain-behaviour correlations in the current study may be the disease staging of our participants. In Study 1, I failed to identify any associations between white matter microstructure and my indices of tau pathology, suggesting that, as a group, the current participant sample may be a lower risk for emergence of the clinical syndrome. Tau deposition has been directly related to cognitive performance (Bejanin et al., 2017; Jack, 2012; Xia et al., 2017) and changes in axonal packing density, related to tau deposition, have been related to cognitive decline (Tian et al., 2023). As such, the current study cohort may not carry sufficient pathological burden, particularly related to tauopathy, to detect associations between white matter microstructure and cognition that are not characteristic of typical aging. Consistent with this idea, a recent longitudinal investigation of preclinical AD suggests that the relationship between tau pathology and white matter may be bidirectional. Specifically, white matter properties (i.e., network efficiency) may moderate the association between tau pathology and cognition and have the potential to mitigate the effects of tau on memory decline (Qiu et al., 2024). Moreover, recent findings suggest that even when AD-related brain changes are present, cognitive decline may not occur unless there is underlying vascular dysfunction. This could further explain why certain individuals in early disease stages maintain cognitive function despite the presence of Aβ pathology (Bagi et al., 2023).

Finally, in considering the absence of brain-behaviour associations here, it is important to consider the limitations of a cross-sectional design which does not allow for consideration of

individual change trajectories as related to alterations in white matter integrity (Jack Jr et al., 2024). This is particularly salient given the current cohort which, by definition, remains within the normal range on cognitive tests, thereby narrowing the range of variability necessary to detect subtle associations.

Conclusion

The findings from Study 2 provide evidence that white matter microstructure is related to cognitive performance in preclinical AD, but rarely over and above normal age-related effects. Future studies are necessary to interrogate these associations in the context of cognitive change, using longitudinal study designs. This approach would help clarify how compensatory mechanisms evolve during early disease stages and their impact on cognitive functions. Additionally, future research should incorporate measures of vascular health given the importance of vascular dysfunction in the emergence of cognitive dysfunction. Incorporating cerebrovascular markers could provide insight into how vascular changes interact with white matter integrity and neurodegenerative pathology to influence cognitive outcomes.

CHAPTER 4

Integrated Discussion

Understanding early brain changes in AD is crucial given that the onset of neuropathological changes can appear years, or possibly even decades, before the emergence of clinical symptoms. Post-mortem and neuroimaging studies have highlighted that white matter abnormalities often precede cortical atrophy and may be an important marker of AD risk and progression. This dissertation examined associations between established markers of AD risk and whole-brain white matter microstructure in asymptomatic individuals at elevated disease risk. Specifically, I utilized a novel approach for assessing white matter integrity *in vivo*, NODDI, that links patterns of diffusion in white matter more closely to putative neurobiological mechanisms of disease progression in a cognitively unimpaired cohort of older adults with first-degree familial risk of AD. Employing a data-driven multivariate statistical model, I conducted two studies to investigate the associations of whole-brain white matter with AD disease risk based on age, APOE4 genotype, CSF and PET biomarkers of Aβ and tau pathology (Study 1), as well as associations with cognitive performance (Study 2).

As predicted, Study 1 demonstrated that increased disease risk is generally associated with reduced axonal packing density (NDI), orientation dispersion reductions in architecturally complex tracts and increases in more uniform tracts (ODI), and free water increases (ISOVF). These patterns were most notably observed with increasing age. When accounting for age, AD risk markers were most associated with axonal packing density variations. As hypothesized, reduced NDI was observed with lower circulating Aβ42, suggesting that amyloidosis primarily impacts axonal packing density in early disease stages. In PET analyses of amyloidosis, NDI was lower in APOE4 carriers, irrespective of their Aβ-PET status (i.e., whether an individual was

identified to be Aβ+ or Aβ-). While NODDI metrics were significantly associated with Aβ pathology markers, they were not associated with CSF or PET biomarkers of tau pathology. In Study 2, NODDI associations with cognitive performance on indices of episodic memory, processing speed, and executive control were examined. As predicted, the associations between NODDI metrics and cognition were subtle, with NDI emerging as the most sensitive indicator of cognitive performance. While previous studies have associated NDI more strongly with executive control, my findings indicate that reductions in axonal packing density are linked to poorer episodic memory performance. While both increases and decreases in ODI were associated with episodic memory and executive control, these associations were not significant after accounting for age. However, these preliminary findings relating ODI to cognition in tract-specific patterns suggest that this measure may provide more specificity with regard to detecting alterations in microstructural integrity that adhere to particular tracts and vulnerabilities to disease (e.g. Wearn et al., 2024). Though prior studies have identified ISOVF associations with executive control, my results suggest that in addition to free water increases, free water decreases specific to brainstem tracts are related to poorer executive control and parallel the ODI findings.

Across the findings of Study 1 and Study 2, three key themes emerged that capture the broader implications of this dissertation. First, chronological age, the most predictive risk factor for AD, was the most robustly associated risk factor with a range of morphological changes associated with lower white matter microstructural integrity. The impact of advancing age was more pronounced than that of any other risk factor examined, potentially suggestive of underlying pathophysiological mechanisms such as neuroinflammation and microvascular changes, as described in Chapter 1. Given the comparatively restricted age range of our sample, this finding underscores NODDI's sensitivity to age-related differences in white matter

microstructure. These results highlight the importance of carefully accounting for aging when examining relationships between NODDI and AD risk factors.

Second, by deconstructing the DWI signal into more biologically plausible compartments, it is possible to enhance both sensitivity and specificity for age- and AD related impacts on white matter microstructure. NDI, a measure of axonal packing density, proved to be the most sensitive of the NODDI metrics to AD risk factors, neuropathology, and cognition. Associations with NDI were observed across the brain in association, commissural, and projection tracts, suggesting that axonal packing density may be a global marker of white mater microstructural alterations in older age and in persons at elevated risk for AD. In contrast, my findings of both increases and decreases in ODI in the context of aging, AD-risk, and cognition suggest that this metric may provide greater spatial specificity coupled to the morphology and architecture of specific fibre tracts. While my ODI findings were less robust than the observed NDI associations, there was convincing evidence for tract-specific associations that should be pursued in the context of tract-specific vulnerabilities to AD pathology, an approach that has recently been described in a separate report from our lab (Wearn et al., 2024).

A third theme highlights the importance of considering interactions among risk factors when examining impacts on microstructural integrity. Specifically, the findings reported in Study 1 revealed interactions between AD pathology and APOE genotype, wherein lower NDI was observed for APOE4 carriers with low Aβ-PET burden, as compared to APOE4 non-carriers, regardless of Aβ status. This finding suggests that APOE4 carriers may experience more pronounced axonal packing density reductions at preclinical stages, potentially reflecting an early vulnerability to AD pathology that is not solely dependent on Aβ burden. This somewhat counterintuitive result suggests complex mechanisms underpin the relationships among AD-risk

factors and white matter microstructure, particularly at the very earliest stage of disease. In this integrated discussion, I will review these three broad themes in more detail and propose an agenda for future research.

AGE IS ASSOCIATED WITH ALTERATIONS IN WHITE MATTER MICROSTRUCTURE

Aging is one of the most significant risk factors for AD (Hou et al., 2019). Consistent with predictions, age was associated with a range of morphological variations in white matter microstructure, as evidenced by significant correlations with all three NODDI metrics: reduced axonal packing density, region-dependent shifts in orientation dispersion, and increased free water. Notably, my results show that advancing age exerts broad morphological effects on white matter microstructure in at-risk individuals, as has been reported elsewhere (Motovylyak et al., 2022). However, I extend these findings by providing the first evidence that age-related impacts on white matter microstructure largely eclipse those associated with other risk factors and largely account for observed associations between white matter microstructure and cognitive performance.

Age-related changes in white matter microstructure are consistent with known features of neuronal physiology, including non-proliferation which limits the capacity for repair and regeneration in response to cumulative cellular damage and structural degradation over time (Frautschy & Cole, 2010; Mattson, 2006). Within neurons, axonal processes are most susceptible to age-related change (Groh et al., 2021; Salvadores et al., 2017), as their length and morphological complexity expose them to increased metabolic demands, vulnerability to oxidative stress, and cumulative structural wear, which can disrupt efficient signalling and connectivity over time (Peng et al., 2021; Wang et al., 2022; Winnubst et al., 2019). In fact, these

vulnerabilities highlight the interplay between normal aging processes and neurodegenerative changes. Beyond their contribution to typical age-related changes, age-related factors are thought to play a critical part in the onset and advancement of AD (Frautschy & Cole, 2010; Mattson, 2006). Accumulating evidence suggests that some of these age-related factors include chronic neuroinflammation and changes to local microvasculature, which can lead to white matter hypoperfusion that may underlie disruptions in AD (Amor et al., 2010; Glass et al., 2010; see Liu 2018 for review). These insights about the vulnerabilities of neurons and the role of neuroinflammation raise important questions about the potential utility of NODDI in elucidating these underlying mechanisms.

NODDI as a Marker of Neuroinflammation in Preclinical AD

Emerging evidence points to distinct microstructural changes occurring at different stages of AD, where early stages may involve neuroinflammation, while later stages are marked by neurodegeneration (Torso et al., 2022; Zhang et al., 2023). Some evidence exists that NODDI metrics can serve as markers of neuroinflammation. Neuroinflammation expands the proportion of water in the extracellular space (Syková & Nicholson, 2008), where immune cells, including microglia, regulate inflammatory effects (Schwartz et al., 2006). This is likely to result in a comparable increase in free water (Kraguljac et al., 2021). In this dissertation, I observed age-related increases in ISOVF, an index of free water. While it is not possible to histologically confirm free water as a marker of inflammation, recent evidence from a transgenic animal model of AD is consistent with this interpretation (Fick et al., 2017).

ODI has also been identified as a possible marker of neuroinflammation. In particular, computational and animal models have demonstrated ODI's sensitivity to microglial density as well as the cellular changes related to microglial activation (Colon-Perez et al., 2019; Yi et al.,

2019). Microglia in the extra-neurite space undergo dynamic changes in density and morphology throughout all stages of neuroinflammation (Yang et al., 2013). It has been hypothesized that these microglial changes could in turn affect water diffusivity in the extra-neurite space (Yi et al., 2019), presumably affecting the organization and dispersion of nearby axons.

NDI has also been flagged as a potential marker of neuroinflammation. In a study examining participants across the AD spectrum, NDI was associated with a CSF marker of inflammation. However, this association disappeared when preclinical participants were examined independently of symptomatic individuals (i.e., MCI and AD). These findings raise questions about the sensitivity of NODDI to neuroinflammation at early disease stages, as evidence to date has been limited to non-human animal models, with no reports of similar associations in human studies. Alternatively, this discrepancy may reflect differences in the markers used or suggest that neuroinflammation could be a secondary process rather than a core pathological mechanism responsible for white matter dysfunction at the very earliest, preclinical stages of AD. A recent report provides provisional support for the latter hypothesis, suggesting that myelin dysfunction in the aging brain leads to microglial activation, which subsequently causes the neuroinflammatory cascade that prevents clearance of Aβ deposits (Depp et al., 2023). NODDI may offer a viable avenue for tracking neuroinflammation, especially as research efforts move toward clinical interventions aimed at regulating the inflammatory response (Ferretti et al., 2012). However, caution is advised given that NODDI metrics were not originally developed to interrogate neuroinflammatory changes (Yi et al., 2019).

NODDI as a Marker of Microvascular Alterations in Preclinical AD

In addition to neuroinflammation, age-related alterations in the brain's microvasculature can heighten white matter's susceptibility to hypoperfusion (Agarwal & Carare, 2021). Over time this may result in compromised perivascular drainage throughout the brain, ultimately reducing the clearance of Aβ (Brown & Thore, 2011). Evidence suggests that these alterations in microvasculature are likely secondary contributors to white matter microstructural changes. Although microvascular-related white matter damage precedes cortical atrophy (Brun & Englund, 1986; Englund, 1998; Sjobeck et al., 2006), recent research links early alterations in genes to myelin proteins specific to AD (Ferrer & Andrés-Benito, 2020). Some evidence exists that NODDI metrics, particularly ISOVF and NDI, may be sensitive to changes in local microvasculature. For instance, capillary blood flow may influence the free water fraction in the brain (Rydhög et al., 2017). However, further research is needed to clarify how changes in blood flow in diseased states can affect free water or ISOVF measurements. Blood vessel density in periventricular areas declines with both normal aging and AD (Brown & Thore, 2011), consistent with reports of reduced blood flow to white matter (Schuff et al., 2009), potentially leading to hypoxic or ischemic damage. My findings of age-related increased periventricular free water may indirectly reflect this process. Another study observed that ISOVF and NDI increases in the genu of the corpus callosum were reflective of vascular-related white matter alterations in older adults and in part, predicted cognition (Raghavan et al., 2022). My findings indicate that the associations between white matter microstructure and cognition were also predominantly accounted for by age. Emerging evidence suggests that microvascular changes underlie the transition to clinical symptoms (Bagi et al., 2023; Finsterwalder et al., 2020), reinforcing the notion that microvascular mechanisms could be secondary contributors in the context of

preclinical AD. Given that the susceptibility to vascular disease increases with age, future studies should account for vascular risk factors and examine microvascular markers within the context of preclinical AD to disentangle their impact from the effects of typically advancing age (Curtis et al., 2018; North & Sinclair, 2012; Rodgers et al., 2019).

NDI IS AN EARLY INDICATOR OF WHITE MATTER MICROSTRUCTURAL INTEGRITY IN ELEVATED AD-RISK

Among the NODDI metrics, NDI most often exhibited associations with established markers of disease risk and cognition, including age, CSF Aβ42, interactions between APOE4 and Aβ-PET, and episodic memory. This suggests that axonal packing density may be the most vulnerable to AD-related pathology, potentially representing the earliest morphological change in white matter microstructure. This finding builds on studies comparing NODDI and DTI metrics across the AD spectrum. Previous studies have demonstrated that NDI outperforms FA in detecting AD-related changes, particularly with respect to differentiating individuals at earlier stages of the disease (e.g., preclinical vs. MCI) (Fu et al., 2020). Moreover, NDI outperforms other NODDI metrics in its sensitivity to disease pathology indexed by PET (Raghavan et al., 2021; Wen et al., 2021) and CSF biomarkers (Moody et al., 2022). In preclinical research involving cognitively unimpaired individuals at higher risk for AD, NDI's sensitivity to aging effects has been pronounced, especially in key regions such as the genu of the corpus callosum and the cingulum-corpus callosum (Merluzzi et al., 2016; Motovylyak et al., 2022).

NDI as a Marker of Demyelination

Axonal degeneration and demyelination are both contributors to, and predictors of, white matter abnormality severity in AD (McAleese et al., 2017). As highlighted in recent reviews (Maitre et al., 2023; Nasrabady et al., 2018), research suggests that although oligodendrocytes

continue producing myelin with age, the resulting sheaths may be thinner, and the internodes may be shorter (Marner et al., 2003), likely contributing to the observed reductions in axonal packing density seen with advancing age in my study. Myelinated axons have been found to decrease in length by 10% with each decade from age 20 to 80 (Marner et al., 2003). Indeed, NDI reductions in aging have been shown to parallel patterns of demyelination (Depp et al., 2023), indexed by the myelin water fraction (Qian et al., 2020). Even more recently, it has been suggested that NDI reductions in preclinical AD may reflect age- or AD-related atrophy of neuromelanin-containing cells (Wearn et al., 2024). Furthermore, thinner myelin sheaths and shorter axons may cause white matter dysfunction by impairing signal conduction and increasing susceptibility to injury, oxidative stress, or Aβ-related damage (Bartzokis, 2011). My findings of NDI associations with CSF Aβ42, in addition to advancing age, aligns with this model.

NDI as a Marker for AD Detection and Progression

Preserved myelination is critical for complex cognition, including memory consolidation (Chen et al., 2020; Steadman et al., 2020), in later life. This study provides further empirical support for this idea demonstrating that NDI is the most sensitive of the NODDI metrics to changes in cognition, including episodic memory (Gozdas et al., 2021; Motovylyak et al., 2022; Raghavan et al., 2021; Slattery et al., 2017), highlighting its potential as a marker for early disease detection and staging. Further, among diffusion metrics (including DTI), NDI is the most sensitive to group differences (cognitively unimpaired vs. MCI vs. dementia), with reductions in NDI correlating with increased disease severity (Fu et al., 2020).

The improved *sensitivity* and *specificity* offered by NODDI can support more accurate diffusion-weighted estimates of white matter microstructural alterations resulting from

pathophysiological processes related to AD such as demyelination, axonal damage, neuronal loss, and inflammation (Aye et al., 2022; Ehrenberg et al., 2018; Weiskopf et al., 2013).

AXONAL PACKING DENSITY LINKED TO APOE GENOTYPE AND AMYLOID DEPOSITION

This dissertation is among the first to explore the relationship between APOE4 and NODDI metrics in the context of preclinical AD. APOE4 is the prominent genetic risk factor for sporadic AD, largely due to its importance in myelin regulation (Blanchard et al., 2022). DTI investigations of APOE4 carriers have yielded mixed results regarding white matter changes in cognitively unimpaired older adults. While some studies report significant alterations in diffusion metrics (Lopez et al., 2003; Petersen et al., 2014; Ungar et al., 2014), others note null findings (Kryscio et al., 2006; Tervo et al., 2004), or inconsistent results (Boyle et al., 2010). Indeed, I did not observe any associations between APOE4 and NODDI in Study 1. However, epidemiological research on preclinical AD has established a link between Aβ pathology and APOE genotype (Jansen et al., 2022; Jansen et al., 2015). I extend these findings by demonstrating for the first time that white matter microstructural dysfunction is isolated to APOE4+ individuals without Aβ burden (indexed by PET), distinguishing this unique group from the APOE4- Aβ- and APOE4- Aβ+ groups. My findings suggest that axonal packing density reductions at preclinical stages are specific to APOE4 carriers with below-threshold Aβ burden, compared to APOE4 non-carriers, regardless of non-carrier Aβ status.

Although APOE4 is associated with increased disease risk, carriers of APOE2 have a reduced risk, with studies suggesting that this protective effect is stronger in women than men (Neu et al., 2017). More recently, research has expanded to explore white matter changes, revealing that the antagonistic effects of APOE2 and APOE4 on white matter microstructure

appear predominantly in women (Reas et al., 2024). This interplay between APOE genotype, sex, and Aβ status may help explain some of the nuances in my findings. Future research with larger and more balanced samples will be essential to fully understand the differential effects of APOE2 and APOE4, as well as sex-specific variations in white matter microstructure and AD risk.

Limitations & Methodological Considerations

There were several limitations in this dissertation that will be important to address in future research. A major limitation is the cross-sectional and correlational nature of these studies, which prevents me from drawing conclusions about causality from these results and does not allow for tracking individual trajectories over time. Longitudinal studies, ideally with post-mortem histological evaluation, can assist in attributing NODDI alterations to specific tissue properties and to characterize disease progression in early stages of AD.

Given the sample used in this dissertation was mostly female, I was unable to explore sex differences. As noted earlier, future work with more balanced sample sizes for biological sex will be needed to characterize sex-differences in the morphology of white matter microstructure at preclinical stages of AD. More research is required to understand sex interactions with APOE genotypes, and disease burden. In addition, the sample consisted of predominantly Caucasian participants. To adequately predict risk and disease progression cross-culturally, it will be crucial for future studies to sample more broadly across various races and ethnicities. Disparities in AD prevalence among population subgroups have been repeatedly demonstrated (Matthews et al., 2019) and research evidence suggests significant differences in biomarker profiles for different races and ethnicities (Rosselli et al., 2023).

An Agenda for Future Research

This dissertation provides the first comprehensive examination of white matter microstructure in relation to established AD risk factors and cognitive functioning within a single cohort of at-risk older adults. White matter microstructural changes have been shown to precede grey matter changes in AD. Understanding these changes is therefore imperative for treatment and intervention in AD. The rapid growth of the elderly population is the dominant demographic trend in the 21st century. AD is emerging as the most prevalent neurodegenerative disorder affecting this age group and the primary cause of dementia worldwide (Alzheimer's Association, 2024; NIA, 2023). Dementia ranks as the seventh leading cause of death and significantly contributes to disability and dependency among older adults globally (NIA, 2023). According to the World Health Organization (2023), approximately 55 million people are living with dementia, with an estimated 10 million new cases each year. Given this rising prevalence, promoting healthy aging and preventing neurodegenerative disease has become an international priority.

In this context, this dissertation sought to provide a comprehensive and biophysically meaningful examination of white matter microstructure in the preclinical stages of AD. The findings reveal that significant alterations in axonal morphology are detectable before marked cognitive decline occurs, highlighting the potential for early intervention. My research implemented a novel and clinically feasible DWI technique, offering a more sensitive and specific lens for detecting neurodegenerative changes compared to conventional methods, one that can be readily implemented in clinical settings. By employing multivariate and data-driven statistical analyses, I was able to characterize patterns of whole-brain microstructure in relation to established markers of disease risk and cognition. Notably, age emerged as a critical risk

factor, associated with a broad range of microstructural changes in axonal morphology. NODDI's ability to detect these age effects even within a limited age range emphasizes the importance of accounting for age-related effects in future investigations of AD risk using NODDI methods. Axonal packing density, as measured by NDI, proved to be particularly sensitive to AD pathology and risk factors, underscoring its vulnerability during preclinical stages and potential as a staging biomarker. The interplay between amyloid-beta pathology and genetic predisposition was also found to influence the most pronounced changes in white matter morphology. Despite these morphological shifts, their impact on cognition remains subtle in preclinical stages, suggesting the presence of compensatory mechanisms that may delay the emergence of cognitive symptoms.

By relating biophysically meaningful metrics of white matter microstructure to already-established biomarkers of disease risk, I aim to support the search for accurate and sensitive *in vivo* markers of neurodegeneration. Such markers are vital for identifying preclinical individuals at risk for developing AD long before the onset of clinical symptoms, potentially aiding in characterizing the staging and progression of the disease. Given its non-invasive nature, neuroimaging serves as a valuable tool for early detection and monitoring of AD, especially when compared to current biomarker gold standard such as cerebrospinal fluid (CSF) analysis, which involves highly invasive lumbar puncture techniques.

The absence of effective pharmacological treatments that can slow or stop the progression of AD suggests that dementia may represent a stage of the disease in which neurodegeneration has advanced too far for effective interventions. Therefore, characterizing the earliest pathological changes in the disease process provides an opportunity to target these initial phases, maximizing the potential impact of emerging or yet-to-be-discovered interventions.

Although white matter changes have been less studied as potential biomarkers, their profound implications in the early stages of AD warrant further exploration. By focusing on these early white matter changes, this research aims to contribute to the scientific literature and enhance early detection and intervention strategies for AD, ultimately supporting the goal of promoting healthy aging.

Given the non-linear trajectories of diffusion metrics from middle- into later- and older-adulthood, longitudinal measures of both white matter and cognitive abilities are imperative to distinguish normal aging from AD at the very earliest emergence of neuropathology and progressing into prodromal and clinical disease stages. Moreover, as the findings of this dissertation clearly demonstrate, differentiating age-related changes from asymptomatic AD remains a critical challenge for understanding when and how normal aging transitions to a pathological course towards the emergence of the clinical syndrome.

Research ongoing with the PREVENT-AD cohort offers much hope in this regard. Data collection is ongoing, with repeat assessments of both DWI and cognition moving to completion. Longitudinal data will allow for more complex modeling of the lead and lag associations between white matter integrity, AD risk factors, and cognition. Moreover, techniques to derive plasma-based markers of AD risk are advancing at an exceptional pace, enabling quantification of disease risk from simple blood draws. Such advances are critically necessary to stratify participants by disease risk across the continuum from normal to pathological aging. These plasma-based methods are much less invasive and feasible to obtain clinically, enabling researchers to more readily map neurobiological changes, including changes to white matter microstructure, to disease risk with greater temporal precision (alignment of brain-behaviour-biomarker data collection) and resolution (higher frequency sampling of disease risk). Moreover,

with continuing longitudinal data collection, an increasing proportion of this at-risk cohort is transitioning to prodromal and clinical stages of AD. While this represents a personal tragedy for the participants and their families, one that brings into clear focus the immense contribution these individuals have made towards solving the puzzle of AD, it opens a unique window for identifying the most potent predictors of transition to the clinical syndrome. As this dissertation has demonstrated, alterations in white matter microstructure are likely an early occurring, and critically important piece of that puzzle.

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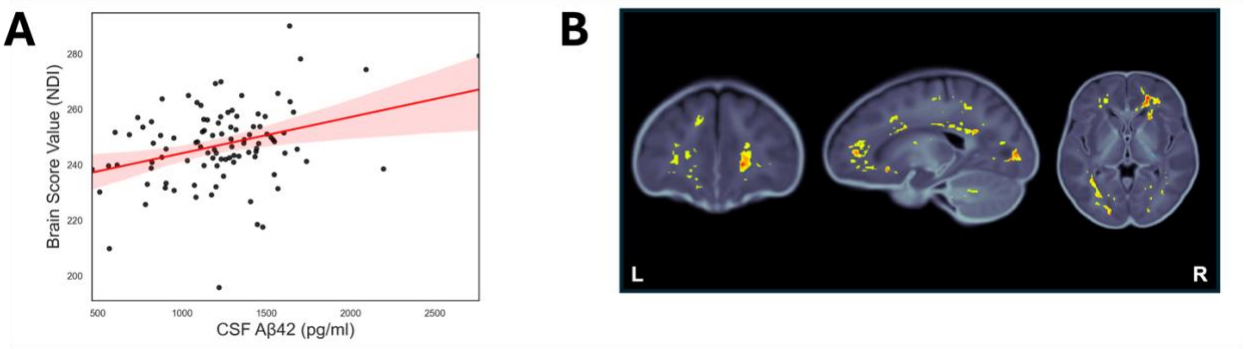
Appendix A

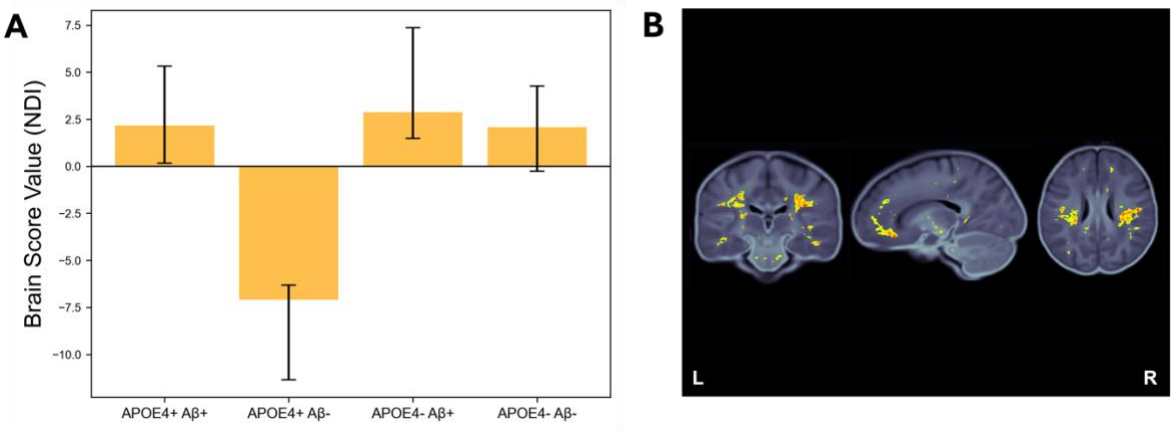
Non-Age Residualized PLS Analysis Results of NDI Associations with CSF Aβ42



Note: Figure details as described in Figure 2.4.

Appendix B

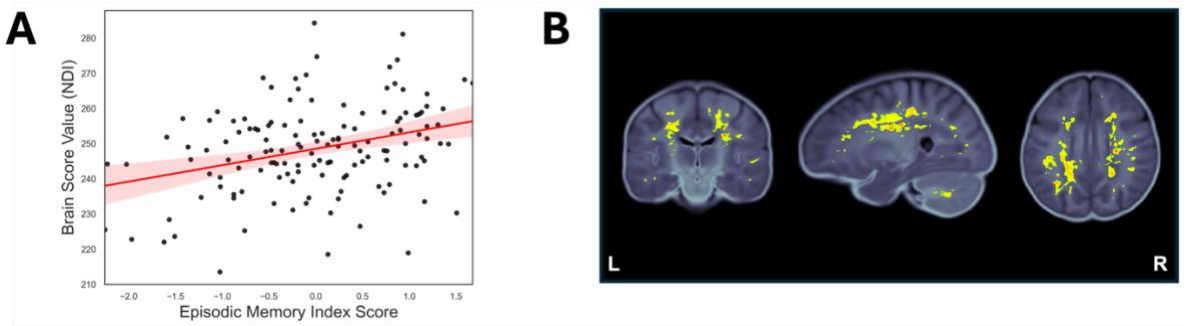
Non-Age Residualized PLS Analysis LV1 Results for NDI Associations with APOE4/Aβ-PET



Note: Figure details as described in Figure 2.5.

Appendix C

Non-Age Residualized PLS Analysis Results of NDI Associations with Episodic Memory



Note: Figure details as described in Figure 3.1.

Appendix D

Brain Coordinates for the NDI by Age PLS Analysis

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Uncinate Fasciculus	Right	38	5	-29
Forceps Minor	Left	-18	32	18
	Right	17	31	18
Superior Longitudinal Fasciculus	Left	-33	-44	27
	Right	36	-41	26
Anterior Thalamic Radiations	Left	-23	32	13
	Right	22	25	16
Inferior Fronto-Occipital Fasciculus	Left	-21	25	2
	Right	22	25	-1
Corticospinal Tract	Left	-23	-17	37
	Right	22	-27	44
Cerebellum	Left	-19	-69	-39
	Right	22	-63	-41

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway.

Appendix E

Brain Coordinates for the ODI by Age PLS Analysis

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Corticospinal Tract	Left	-25	-19	25
	Right	25	-19	25
Inferior Fronto-Occipital Fasciculus	Left	-22	23	3
	Right	22	25	-1
Anterior Thalamic Radiations	Left	-23	18	13
	Right	23	18	13
Forceps Minor	Left	-19	40	11
	Right	19	40	10

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway.

Appendix F

Brain Coordinates for the ISOVF by Age PLS Analysis

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Cingulum	Left	-8	17	18
	Right	8	17	18
Inferior Longitudinal Fasciculus	Left	-41	-34	-10
	Right	42	-34	-10
Forceps Minor	Left	-7	28	5
	Right	7	28	5
Inferior Fronto-Occipital Fasciculus	Left	-35	-55	2
	Right	35	-55	2
Corticospinal Tract	Right	23	-19	41
Unidentified Tract 1	Right	33	-3	39
Unidentified Tract 2	Left	-25	-3	37
	Right	25	-6	37

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway. Unidentified Tract 1 is visually proximal to the right superior longitudinal fasciculus. Unidentified Tract 2 is proximal to the superior longitudinal fasciculus and the corticospinal tract.

Appendix G

Brain Coordinates for the NDI by CSF Aβ42 PLS Analyses

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Forceps Minor	Right	20	37	7
Forceps Major	Left	-18	-89	2
Anterior Thalamic Radiations	Right	23	37	7
Superior Longitudinal Fasciculus	Left	-47	-13	23

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway across both original and age-residualized images.

Appendix H

Brain Coordinates for LV1 of the NDI by APOE4/Aβ-PET PLS Analyses

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Superior Longitudinal Fasciculus	Left	-36	-25	29
	Right	36	-25	30
Corticospinal Tract	Left	-26	-25	35
Forceps Minor	Left	-17	48	2
	Right	18	48	11
Inferior Longitudinal Fasciculus	Left	-42	-20	-15
	Right	42	-12	-17

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway across both original and age-residualized images.

Appendix I

Brain Coordinates for the NDI by Episodic Memory PLS Analyses

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Corticospinal Tract	Left	-26	19	27
	Right	26	-19	30
Superior Longitudinal Fasciculus	Left	-37	-19	27
	Right	37	-19	29
Forceps Minor	Left	-12	32	4
	Right	12	32	4

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway across both original and age-residualized images.

Appendix J

Brain Coordinates for the ODI by Episodic Memory PLS Analysis

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Forceps Minor	Right	12	36	6
Corticospinal Tract	Left	-25	0	22
	Right	25	0	22
Inferior Fronto-Occipital Fasciculus	Left	-37	-26	-3
	Right	37	-26	-3
Cerebellum	Left	-15	-47	-31
	Right	15	47	31

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway.

Appendix K

Brain Coordinates for the ODI by Executive Control PLS Analysis

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Corticospinal Tract	Left	-22	-17	15
	Right	23	-18	16
Inferior Longitudinal Fasciculus	Left	-33	-69	2
	Right	38	-53	-1
Cerebellum	Left	-29	-48	-39
	Right	29	-48	-39
Superior Longitudinal Fasciculus	Left	-40	29	32
	Right	35	-29	33
Brainstem	Left	-6	-24	-12
	Right	6	-24	-14
Unidentified Tract	Left	-17	22	33

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway. Unidentified Tract is located superior to the forceps minor and cingulum in the left hemisphere.

Appendix L

Brain Coordinates for the ISOVF by Executive Control PLS Analysis

		MNI Coordinates		
Fibre Bundle Location	Hemisphere	X	Y	Z
Forceps Major	Left	-34	-65	12
Superior Longitudinal Fasciculus	Left	-34	-40	31
	Right	34	-38	29
Cingulum	Left	-10	27	19
Brainstem	-	0	-26	-28

Note. White matter pathways and the associated coordinates were identified based on visual inspection using the JHU atlas. MNI coordinates in table represent the peak bootstrap ratio that could be visually identified within a given pathway.