DISSERTATION

NEW EVIDENCE FOR AGE DIFFERENCES, WITHIN-PERSON DECLINES AND PLASTICITY IN THE AGING WHITE MATTER: NEW MRI TECHNIQUES AND ANALYTICAL APPROACHES

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ABSTRACT

NEW EVIDENCE FOR AGE DIFFERENCES, WITHIN-PERSON DECLINES AND PLASTICITY IN THE AGING WHITE MATTER: NEW MRI TECHNIQUES AND ANALYTICAL APPROACHES

White matter deterioration leads to cognitive impairments in healthy aging, Alzheimer's disease, and related dementias. Therefore, it is critical to identify interventions that can slow the white matter deterioration. Animal studies have suggested that the white matter plays an active role in brain plasticity and learning. However, evidence for experience-induced plasticity in adult human white matter remains scarce and inconsistent, especially in older age. To accurately predict the effects of interventions on the white matter, we first need to understand the direction and magnitude of naturally occurring within-person changes across adulthood. To date, white matter in aging, Alzheimer's disease, and related dementias have been studied almost solely using diffusion MRI, which provides limited information about the white matter microstructure. Because there is little evidence of white matter plasticity in adult humans, white matter has rarely been considered as a target for interventions against dementia.

This dissertation comprises three scientific articles investigating the mechanisms of white matter decline and plasticity. The first article presents a study using a novel technique (T1w/T2w imaging) to examine the effects of aerobic exercise on aging white matter in a randomized controlled trial. The second article is a meta-analysis and systematic review of within-person changes in white matter. The third article shows the first application of a multimodal fusion analysis to study healthy aging white matter. Through these innovative approaches, this

dissertation provides new insights into the mechanisms of white matter decline and plasticity, paving the way for the development of effective interventions to promote healthy brain aging.

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DEDICATION

A mi abuela Betty, tu amor y tu bondad me acompañan todos los días.

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CHAPTER 1

1.2. Introduction

According to the Alzheimer's Association, an estimated 6.5 million Americans aged 65 and older are affected by Alzheimer's disease and related dementias ("2022 Alzheimer's Disease Facts and Figures," 2022). In addition, an estimated 8 million Americans suffer from mild-cognitive impairment. Among those with MCI, about 15% develop dementia after two years (Petersen et al., 2018). Despite significant efforts to develop treatments for these conditions, existing approaches targeting gray matter pathology have proven largely ineffective. Research on white matter aging and its impact on cognitive decline has the potential to significantly advance our understanding of these conditions and contribute to the development of more effective interventions.

In recent years, white matter abnormalities have been increasingly implicated in the progression and risk of Alzheimer's disease, and related dementias (Nasrabady et al., 2018). The integrity of axons or myelin, the key functional components of the white matter, determines the speed and synchrony of neuronal communication and is thus critical for successful information processing (Chorghay et al., 2018). Cortical "disconnection" (Bartzokis, 2004) due to white matter degeneration is considered one of the primary mechanisms of cognitive decline in healthy aging (Bartzokis, 2004; Felts et al., 2018) and may precede grey matter pathology in Alzheimer's disease, and related dementias (Nasrabady et al., 2018). However, the brain's white matter has rarely been considered a target for interventions against dementia.

Accumulating evidence suggests that the adult white matter is more plastic than initially thought (Sampaio-Baptista & Johansen-Berg, 2017). A key contributor to this plasticity is experience-dependent plasticity, which refers to the adaptive changes in white matter structure

and function that occur in response to an individual's life experiences, such as their lifestyle. More and more evidence shows that our experiences can cause changes in the cells that create myelin. For instance, rodent studies have shown experience-dependent changes in the differentiation of myelin progenitor cells (McKenzie et al., 2014; Simon et al., 2011), myelination (Chorghay et al., 2018; Kato et al., 2020), and axonal diameter (Bobinski et al., 2011), which correlate with improved motor skills or cognitive performance (Fields & Bukalo, 2020; Sampaio-Baptista et al., 2013). These findings suggest that interventions targeting white matter plasticity may have the potential to improve cognitive function in aging populations.

However, several neuroimaging studies have reported changes in diffusion tensor imaging (DTI) following cognitive or motor training in young (Scholz et al., 2009; Steele & Zatorre, 2018) and older adults (de Lange et al., 2018; Lövdén et al., 2010). Evidence of experience-induced plasticity in adult human white matter microstructure is still scarce and inconsistent (Sampaio-Baptista & Johansen-Berg, 2017). As white matter within-person change and decline can occur over a relatively short period (Burzynska et al., 2017; Mendez Colmenares et al., 2021); it is critical to determine whether white matter deterioration is reversible or malleable. Better understanding how the white matter changes as we age can help us develop targeted interventions for promoting healthy aging and potentially slowing down cognitive decline in older adults.

1.3. Background

In humans, white matter microstructure in healthy aging, mild-cognitive impairment and dementia has been studied predominantly with DTI and related methods. Previous studies have established that age-related differences in white matter mediate cognitive decline associated with aging, an association referred to as the “disconnection hypothesis” (Bennett & Madden, 2014).

The structural disconnection hypothesis posits that age-related white matter deterioration leads to the disintegration of distributed neural networks, disrupting the communication between different brain regions and impairing their functional integration. Such a breakdown in connectivity affects both local and long-range networks and can result in deficits in various cognitive domains, including attention, memory, language, and executive function.

How do we study the human white matter?

To date, white matter microstructure in aging, Alzheimer's disease, and related dementias have been studied almost solely using diffusion MRI, predominantly DTI (Harrison et al., 2020; Madden et al., 2012). DTI allows to examine the magnitude and directionality of water diffusion within a white matter voxel, which is a three-dimensional unit of volume in a brain MRI. The most commonly used metric in DTI, fractional anisotropy (FA), is a measure of the directional dependence of diffusion (Pierpaoli & Basser, 1996) and is influenced by the fiber orientational coherence, fiber diameter, integrity, and density (Beaulieu, 2002). A second measure of diffusivity is the mean diffusivity (MD), which indicates the overall magnitude of diffusion within a voxel. MD is determined by microstructural elements that may hinder diffusion in any direction, such the permability of cellular membranes. Finally, radial diffusivity (RD) measures the magnitude of diffusion perpendicular to the primary orientation of white matter tracts, which in white matter is restricted by axonal and myelin membranes, while axial diffusivity (AD) is a measure of diffusion along the length of an axon and is thought to reflect chronic axonal injury. However, interpreting the neurobiological mechanisms of altered DTI parameters is not straightforward, because the cellular and molecular processes that determine the diffusivity of water within a voxel can vary across different brain regions. These processes include axonal integrity, permeability of axonal membranes, cytoplasmic transport, and enlargement of

extracellular spaces. Therefore, the degree of anisotropy alone cannot discriminate between the microstructural geometry and integrity of different white matter microstructural elements (Jones et al., 2013).

An alternative white matter imaging method that does not rely solely on diffusion properties is the T1-weighted to T2-weighted (T1w/T2w) ratio. The T1w/T2w ratio is a measure of white matter integrity that has recently gained interest (Sui et al., 2022). It is calculated by dividing the standardized T1-weighted image by the T2-weighted image. This ratio provides an enhanced contrast of myelin in the brain, particularly in the cortex (Glasser & van Essen, 2011).

Given the availability of T1 and T2-w images in existing datasets, the T1w/T2w is a broadly accessible metric for studying white matter decline and plasticity. T1w/T2w has been shown to be sensitive to the vulnerability of white matter in cognitively healthy APOE-4 carriers (Operto et al., 2019), and in demyelinating disorders such as multiple sclerosis (Cooper et al., 2019). However, recent studies have reported correlations between T1w/T2w signals and other white matter elements, such as MRI estimates of axonal diameter (Arshad et al., 2017), axonal density (Fukutomi et al., 2018), and iron content (Shams et al., 2019). Thus, although T1w/T2w may not be specific to any microstructural process, it promises to provide complementary information to DTI or traditional volumetric measures (Uddin et al., 2019).

Theories of white matter aging

Retrogenesis hypothesis of white matter aging

The retrogenesis hypothesis suggests that white matter fibers that develop later in life are more susceptible to degeneration due to aging and Alzheimer's disease, which leads to cognitive deficits. In this context, the term "later in life" refers to the later stages of early development, rather than later adulthood (e.g., after the age of 50). While there is evidence supporting this

hypothesis in relation to Alzheimer's disease (Benitez et al., 2014), it has not been extensively studied in the context of healthy cognitive aging. One of the first studies examining the retrogenesis hypothesis in cognitively healthy adults found that late-myelinating white matter fibers were more vulnerable to age-related white matter deterioration (Brickman et al., 2012b). This susceptibility of late-myelinating fibers had been previously suggested in cross-sectional studies showing age-related change in the genu of the corpus callosum (Bartzokis et al., 2004). Later longitudinal studies found that decreases in FA were substantial in the late myelinating genu of the corpus callosum, while early-myelinating regions such as the superior corona radiata showed little evidence of decreased FA (Barrick et al., 2010; Burzynska et al., 2010b).

Late-myelinating white matter fibers, such as those found in the genu of the corpus callosum, are predominantly located in anterior white matter regions. This distribution is consistent with the anterior-posterior gradient, which suggests that decreases in DTI-FA are more pronounced in anterior white matter regions compared to posterior regions (Bartzokis, 2004; Salat et al., 2005; Sullivan et al., 2010). For example, the effect of age tends to be greater in the anterior regions of the corpus callosum (Head et al., 2004).

Notably, the developmental sequence of myelination is a complex and non-linear process. For example, some regions start myelinating earlier but at a slower pace long into the postnatal period, whereas others myelinate at faster rates over shorter periods (Kinney & Volpe, 2018). Specifically, the sequence of myelination in the central nervous system usually follows a set of "rules" such as rostral to caudal, central to poles (occipital>frontal>temporal), posterior to anterior (in the cerebrum), proximal to distal, and projection before associations fibers (Kinney & Volpe, 2018). DTI data has lent partial support for the retrogenesis hypothesis (Brickman et al., 2012a), as reflected by studies showing steeper age decline in association than projection

fibers (Barrick et al., 2010; Burzynska et al., 2010a) and steeper age decline in the most anterior aspects of the corpus callosum (Bartzokis, 2004; Head et al., 2004; Salat et al., 2005; Sullivan et al., 2010). Still, more longitudinal evidence is needed to better understand the retrogenesis pattern of white matter deterioration in healthy older adults.

Myelin hypothesis of Alzheimer's disease

The central premise of the myelin model is that the developmental trajectory of myelination and its eventual age-related breakdown forms the essence of our uniqueness as a species across all life stages. This model frames the human lifespan in terms of seamless quadratic-like myelination trajectories of spatially distributed neural networks that underlie cognition and behavior. The hypothesis proposes that myelin maintenance and repair endophenotypes are upstream of pathophysiologic mechanisms that produce degenerative diseases such as Alzheimer's disease (Bartzokis, 2011). The myelin model suggets that myelin repair and breakdown occur with (or perhaps are exacerbations of) normal, homeostatic, age-related myelin remodeling processes. In a way, this model suggests that the Alzheimer's disease continuum is defined by pathological changes in grey matter superimposed upon white matter degeneration in aging (Benitez et al., 2022).

Specific aims

This dissertation investigates novel techniques and analytical approaches to examine the decline and plasticity of white matter in healthy aging. By exploring how white matter changes over time, this research aims to offer a more comprehensive understanding of the underlying neural processes contributing to age-related cognitive decline. The specific objectives are to:

Specific aim 1: Investigate if white matter deterioration is reversible or malleable through an examination of experience-dependent plasticity in white matter as a result of an aerobic exercise clinical trial.

Specific aim 2: Understand how white matter changes over time in the aging brain through a systematic review and meta-analysis of longitudinal diffusion MR studies.

Specific aim 3: Explore age differences in white matter microstructure using symmetric data-driven fusion of diffusion tensor MRI.

The following subsections will provide more detail on the specific questions explored in the three manuscripts.

Can we slow down white matter decline?

In the first paper of this dissertation, I examined the effects of a randomized controlled trial of aerobic exercise training on white matter in cognitively healthy older adults. I chose an alternative white matter neuroimaging method (T1w/T2w) that does not rely on the diffusivity properties of tissues.

To inform interventions on how to promote cognitive health, we must consider the extent to which modifiable lifestyle factors can influence the course of white matter aging. The cognitive trajectory associated with normal cognitive aging varies across individuals, and is influenced by individual differences in biological, genetic, health, environmental, and lifestyle factors. Lifestyle factors such as physical activity provide extensive cardiovascular benefits (Booth et al., 2012). Much less is known about the effects of physical activity on the progression of structural brain changes associated with cognitive aging, specifically, changes in white matter.

Clinical trials suggest that aerobic exercise may be the most effective way to broadly improve cognitive function (Kramer & Colcombe, 2018) and brain functional connectivity (Voss et al., 2016), and reverse age-related brain atrophy (Erickson et al., 2011). However, randomized

controlled trials in cognitively normal older adults (Burzynska et al., 2017; Clark et al., 2019; Voss et al., 2013), as well as individuals with mild cognitive impairment or at risk of Alzheimer's Disease (Fissler et al., 2017; Tarumi et al., 2020; Venkatraman et al., 2020), have reported no benefits of 6- to 24-month aerobic exercise interventions on fractional anisotropy in white matter.

Invalid or inconsistent measurement is one possible explanation for the failure of studies to show positive benefits of aerobic exercise on white matter health. Specifically, white matter diffusivity properties are affected by multiple aspects of tissue microstructure, such as myelin or axonal integrity, microstructural geometry (e.g., caliber of axons, myelin g-ratio), and fiber orientational coherence. Therefore, DTI parameters are hard to interpret where fibers cross (Jeurissen et al., 2013; Jones et al., 2013), namely, in 60–90% of white matter voxels (Jones et al., 2013). DTI alone may not be ideal for detecting subtle changes in myelination or fiber organization. Therefore, complementary imaging techniques are needed to comprehensively study adult white matter plasticity. This dissertation contributes to this gap by investigating if white matter deterioration is reversible or malleable through an examination of experience-dependent plasticity in white matter as a result of an aerobic exercise clinical trial. To do this, we will use the T1w/T2w ratio as a complementary magnetic resonance imaging MRI tool that is independent of the diffusion properties of tissues. By using this MRI technique, we hope to gain a more comprehensive understanding of the effects of aerobic exercise on white matter health and determine if it is possible to reverse or slow down age-related white matter deterioration through aerobic exercise.

How does white matter decline over time?

The second paper summarizes evidence from longitudinal *in vivo* MRI studies on within-person changes that naturally occur in the white matter of healthy older adults. To answer this

question, we used DTI, considered the gold standard MRI tool for studying within-person white matter changes.

White matter changes dynamically throughout the lifespan (Engvig et al., 2012; Sampaio-Baptista & Johansen-Berg, 2017). Cross-sectional studies have found nonlinear trajectories in diffusion parameters across the lifespan, suggesting protracted development or myelination until middle adulthood. Specifically, FA has been shown to peak between 20 and 42 years of age, followed by a decline in older age (Lebel et al., 2012). Most longitudinal DTI studies have shown that advancing age is associated with an accelerated decline in white matter microstructure (Beck et al., 2021; Bender & Raz, 2015), while others have reported no significant change in DTI over time (Kocevska et al., 2019). Other longitudinal studies have suggested that within-person changes in white matter tracts are region-dependent (Mayo et al., 2017).

However, it is unclear to what extent within-person changes in aging white matter can be detected using DTI; a meta-analysis on within-person changes in aging white matter has not been conducted. Moreover, the extent to which white matter declines over time or accelerates with age has not yet been systematically reviewed. Finally, the patterns of white matter decline among different brain regions have not been explored in a meta-analysis. Given that it is possible that white matter adapts and changes, even at an older age, understanding the naturally occurring within-person changes in the white matter is critical for better understanding healthy aging, as well as for designing and evaluating the outcomes of clinical trials. This dissertation contributes to this aim by conducting a comprehensive qualitative review of longitudinal DTI studies and performing a meta-analysis on a subsample of studies that provided sufficient data. The findings of this meta-analysis will provide valuable insights into the within-person changes in white

matter microstructure in older age and how these changes may be influenced by various factors such as age, sex, and lifestyle factors. By better understanding these naturally occurring changes in white matter, we can gain a deeper understanding of healthy aging and improve the design and evaluation of clinical trials aimed at promoting healthy aging.

How can we overcome the limitations of a single MRI technique?

Finally, in the third paper, I shift the focus from using a single MRI technique to characterizing aging white matter using multiple diffusion MRI modalities and integrating them using a multimodal fusion approach. This study aims to demonstrate the first application of data-driven symmetric fusion analysis to explore age differences in adult white matter.

Clearly, no single MRI technique – even the most advanced – can fully characterize brain tissue (Calhoun & Sui, 2016). Combining multiple image types or "feature maps" can provide a more rigorous and interpretable characterization of age differences in the white matter.

Because white matter aging is not uniform, but characterized by region-specific patterns (Bennett et al., 2009; Burzynska et al., 2010a, 2017). Multi-modal symmetric fusion analyses can aid identify patterns of correlated group differences across distinct image types. Multi-modal fusion analyses have shown to improve diagnostic classification between healthy controls and patients at different stages of Alzheimer's disease, as recently demonstrated using DTI parameters (Konukoglu et al., 2016) and additional metrics of fiber orientation and structural connectivity (Doan et al., 2017). Other studies using data-driven symmetric fusion approaches showed that multimodal features combining DTI, structural, and relaxometry MRI predicted brain age with better accuracy than any single modality (Cherubini et al., 2016; Groves et al., 2011; Richard et al., 2018). Together, these studies show that symmetric multimodal fusion can provide new and potentially more rigorous information about brain aging and reveal associations

that cannot be identified with a single MRI modality. However, no studies have explored the use of multimodal fusion in the white matter space to study mechanisms of brain aging.

This dissertation shows the results from the first multimodal fusion analyses exploring age differences in white matter microstructure using diffusion tensor MRI. By combining multiple image types or "feature maps" through multi-modal symmetric fusion analyses, we aim to identify patterns of correlated group differences across distinct image types and provide a more rigorous and interpretable characterization of age differences in white matter. By applying this approach to the study of white matter aging, we hope to gain new insights into the mechanisms underlying healthy aging and reveal associations that cannot be identified with a single MRI modality.

CHAPTER 2

WHITE MATTER PLASTICITY IN HEALTHY OLDER ADULTS: THE EFFECTS OF AEROBIC EXERCISE

2.1. Overview

White matter deterioration is associated with cognitive impairment in healthy aging and Alzheimer's disease. It is critical to identify interventions that can slow down white matter deterioration. So far, clinical trials have failed to demonstrate the benefits of aerobic exercise on adult white matter using diffusion Magnetic Resonance Imaging. Here, we report the effects of a 6-month aerobic walking and dance interventions (clinical trial NCT01472744) on white matter integrity in healthy older adults (n=180, 60–79 years) measured by change in the ratio of calibrated T1- to T2-weighted images (T1w/T2w). Specifically, aerobic walking and social dance interventions resulted in positive change in the T1w/T2w signal in late-myelinating regions, as compared to widespread decreases in the T1w/T2w signal in the active control. In addition, adding white matter lesion volume as a covariate in longitudinal analyses did not impact the treatment effect. Notably, in the aerobic walking group, positive change in the T1w/T2w signal correlated with improved episodic memory performance. Lastly, intervention-induced increases in cardiorespiratory fitness did not correlate with change in the T1w/T2w signal. Together, our findings suggest white matter regions that are vulnerable to aging retain some degree of plasticity that can be induced by aerobic exercise training. In addition, we provided evidence that the T1w/T2w signal may be a useful and broadly accessible measure for studying short-term within-person plasticity and deterioration in the adult human white matter.

2.2. Introduction

Global incidence of dementia is projected to double every 20 years (Mayeux and Stern, 2012), thus developing effective strategies to reduce the risk of cognitive decline is critical. Cortical "disconnection" due to white matter degeneration is considered one of the primary mechanisms of cognitive decline in healthy aging (Bartzokis et al., 2004) and may precede grey matter pathology in Alzheimer's disease (Nasrabady et al., 2018). White matter integrity decreases in healthy aging and dementia, as demonstrated by studies using diffusion tensor imaging (DTI) (Madden et al., 2012). As within-person declines in white matter integrity can occur over a period as brief as 6 months in cognitively healthy older adults (Burzynska et al., 2017), it is critical to determine whether white matter deterioration is reversible or malleable.

It is commonly believed that white matter is not involved in adult neuroplasticity; however, studies in rodents have shown experience-dependent changes in oligodendrocyte differentiation (McKenzie et al., 2014; Simon et al., 2011), myelination (Chorghay et al., 2018; Kato et al., 2020), and axonal diameter (Bobinski et al., 2011), which correlated with improved motor and cognitive performance (Fields and Bukalo, 2020; Sampaio-Baptista et al., 2013). To date, there is little evidence of such plasticity in adult humans. Few DTI studies have reported increases in FA following motor training in healthy young adults (Lakhani et al., 2016) and cognitive training in older adults (de Lange et al., 2018; Lövdén et al., 2010). Several randomized controlled trials (RCT) in healthy older adults (Burzynska et al., 2017; Clark et al., 2019; Voss et al., 2013) or individuals with mild cognitive impairment or at risk of Alzheimer's Disease (Fissler et al., 2017; Tarumi et al., 2020; Venkatraman et al., 2020b), have reported no benefits of 6- to 24-month aerobic exercise interventions on white matter fractional anisotropy. This is surprising given the well documented positive effects of aerobic exercise interventions on

cognitive function (Kramer and Colcombe, 2018), brain functional connectivity (Voss et al., 2016), and brain volumes (Erickson et al., 2011). As a result, white matter has rarely been considered as a target for interventions against Alzheimer's Disease and related dementias.

Fractional anisotropy is affected by multiple aspects of tissue microstructure (Jones and Cercignani, 2010). Therefore, it may not detect subtle changes in myelination or axonal health. There has been recent interest in using the ratio of the standardized T1 and T2-weighted images (T1w/T2w) as a measure of white matter integrity (Ganzetti et al., 2014). The phenomenon underlying the grey matter-white matter contrast in T1-w and T2-w images arise from the differences in the T1 and T2 relaxation properties of tissues (Sharma and Lagopoulos, 2010). In the white matter, the proton spins collide with macromolecules and myelin sheaths with hydrophobic properties, limiting water displacement, resulting in shorter T1 and T2 in white matter compared to the cell somas of the grey matter (Deoni, 2010). Since myelin increases signal in T1-w images but decreases signal in T2-w images it has been proposed that the division of the T1-w image by the T2-w image can provide an enhanced myelin contrast, especially in the cortex (Glasser and van Essen, 2011). However, although T1w/T2w has been shown to detect demyelination in multiple sclerosis (Cooper et al., 2019), recent studies reported correlations of the T1w/T2w signal with other elements of the white matter such as MRI estimates of axonal diameter (Arshad et al., 2017), axonal density (Fukutomi et al., 2018), and iron content (Shams et al., 2019). Accordingly, T1w/T2w detected differences in white matter integrity in cognitively healthy APOE-4 carriers (Operto et al., 2019) and in neurodegenerative disorders such as multiple systems atrophy (Sugiyama et al., 2020), which are of mixed etiology. Thus, even though the T1w/T2w may not be specific to any microstructural process, it is promising in providing complementary information to DTI or volumetric measures (Uddin et al., 2019). The

availability of T1 and T2-w images in the existing datasets warrants investigations on cognitive relevance of the T1w/T2w and its ability to detect within-person changes in white matter.

In this study, we compared 6-month change in the T1w/T2w signal in participants randomized to one of three intervention groups: walking, dance, and active control. Our hypotheses were: 1) T1w/T2w signal would decline over 6 months in the control group, similar to earlier DTI findings (Burzynska et al., 2017), 2) Participants in the walking and dance conditions would show positive changes in the T1w/T2w signal compared to the control, 3) Changes in T1w/T2w signal would correlate with positive change in episodic memory, processing speed, executive function (cognitive abilities known to decline with age (Park et al., 2002)), 4) Changes in T1w/T2w would correlate with change in cardiorespiratory fitness (Kramer and Colcombe, 2018). Lastly, given that T1 and T2 relaxations are affected by white matter lesions (as hypo- and hyperintense signal, respectively), which are prevalent in older age (Birdsill et al., 2014), we also explored the impact of white matter lesions on the time-by-group interactions and the effect of time and intervention on white matter lesion volume.

2.3. Methods

Participants

Participants were 247 community-dwelling older adults (average age of 65 yrs., 68% women) enrolled in a 24-week randomized controlled exercise trial that examined the effects of aerobic exercise on cognitive performance and brain health. The trial is registered with United States National Institutes of Health ClinicalTrials.gov (ID: NCT01472744). Individuals were eligible to participate if they met the following inclusion criteria: (a) 60–80 years-old; (b) able to read and speak English; (c) scored <10 on the geriatric depression scale (GDS-15); (d) scored ≥ 75% right-handedness on the Edinburgh Handedness Questionnaire; (e) demonstrated normal or

corrected-to-normal vision of at least 20/40 and no color blindness; (f) low-active, defined as engaging in less than two bouts of moderate-to-vigorous physical activity per week during the last 6 months, each bout lasting <30 min. In addition to this self-reported physical activity, the baseline accelerometer showed that only 0.5% (n=1) of the current sample met the recommendation of at least 150 minutes of moderate-to-vigorous physical activity per week at baseline. Thus, our sample can be defined as low-fit and low-active, but otherwise healthy. (g) local to the study location for the duration of the program; (h) willing to be randomized to one of four interventions; (i) not involved in another physical activity program; and (j) scored >21 on the Telephone Interview of Cognitive Status questionnaire and >23 on the Mini Mental State Exam (Fong et al., 2009). Eligibility also included meeting inclusion criteria for completing a magnetic resonance imaging (MRI) assessment, consisting of: (a) free from neurological disorders affecting the brain such as stroke, TBI, Alzheimer's disease, epilepsy; (b) no history of stroke, transient ischemic attach, head trauma or surgeries including the removal of brain tissue; and (c) no implanted devices or metallic bodies above the waist. Thus, our sample consisted of healthy, community-dwelling, typically low active older adults.

For more information on participant recruitment and screening, see (Baniqued et al., 2018; Burzynska et al., 2017; Ehlers et al., 2017; Fanning et al., 2017; Voss et al., 2018). Participants underwent a series of MRI imaging, cognitive, and cardiorespiratory testing, before and after the 6-month intervention program.

The study was approved by and carried out in accordance with the recommendations of the Institutional Review Board at the University of Illinois at Urbana-Champaign with written informed consent from all participants. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Intervention

After all baseline data were collected, participants were assigned to one of four interventions implemented over four waves from October 2011 to November 2014. Participants were randomized using a computer data management system and baseline-adaptive randomization scheme, taking into account equal distributions of age and gender (Begg and Iglewicz, 1980). Participants in all conditions attended three 1-h exercise sessions per week for 24 weeks (~6 months)(Burzynska et al., 2017; Ehlers et al., 2017). The four intervention groups were as follows: The **active control** involved exercises designed to improve flexibility, strength, and balance with the aid of yoga mats and blocks, chairs, and resistance bands, specifically designed for individuals 60 years of age and older. This intervention served as the active control group to account for the social engagement and novelty in the other interventions, with the difference that the active control was not aimed to increase cardiorespiratory fitness. The **walking** intervention was designed to increase cardiorespiratory fitness. Thus, it involved walking sessions at 50–60% of maximal heart rate, as ascertained from a maximal graded exercise test. Walking duration increased from 20 to 40 min during the first 6 weeks of the program. During the remaining 18 weeks, participants walked for 40 min at 60–75% of their maximal heart rate each session. Frequent assessment of heart rate, using either palpation or Polar Heart Rate Monitors, and rating of perceived exertion ensured that participants' exercise was performed at the prescribed intensity. Exercise logs were completed after each exercise session. The **walking + nutrition** group, in addition to the above walking intervention, received a nutritional supplement containing antioxidants, anti-inflammatories, vitamins, minerals, and beta alanine (Abbott Nutrition, Abbott Park, Illinois). Beta-alanine is thought to promote the effect of increased cardiorespiratory fitness by increasing lean muscle mass. However, the analyses of the primary

outcomes indicated no differences in gain in cardiorespiratory fitness between the walking interventions (Baniqued et al., 2018; Ehlers et al., 2017; Voss et al., 2018) therefore, walking and walking + nutrition were combined for the present analyses. The **dance** intervention was designed to provide simultaneous cognitive and social enrichment combined with aerobic physical activity. The choreographed dance combinations became progressively more challenging over the course of the 6-months program. Group social dance styles were selected to minimize lead-follow roles. In each session, participants learned ~4 dances and recorded their heart rate and perceived exertion after each dance. Each participant learned and alternated between two roles for each dance, increasing the cognitive challenge.

Cardiovascular variables

Cardiorespiratory fitness was assessed before and after the intervention on a motor-driven treadmill by employing a modified Balke protocol (graded exercise test). The protocol involved walking at a self-selected pace with incremental grades of 2-3% every 2 minutes. We continuously collected measurements of oxygen uptake, heart rate and blood pressure. We measured oxygen uptake (VO_2) from expired air samples taken at 30-second intervals until a peak VO_2 (the highest VO_2) was attained; test termination was determined by symptom limitation, volitional exhaustion, and/or attainment of VO_2 peak as established by the American College of Sports Medicine guidelines (American College of Sports Medicine, 2013).

MRI Acquisition

We acquired images on a 3T Siemens Trio Tim system with 45 mT/m gradients and 200 T/m/sec slew rates (Siemens, Erlangen, Germany). T1-weighted images were acquired using a 3D MPRAGE (TR = 1900 ms; TE = 2.32 ms; TI: 900 ms; matrix = 256 × 256; FOV = 230 mm; 192 slices; 0.9 × 0.9 × 0.9 mm^3 voxels size; GRAPPA acceleration factor 2). The non-diffusion

weighted images from the diffusion-weighted acquisition were used as T2-weighted images (b-value = 0 s/mm^2, TR = 5500 ms; TE = 98 ms, matrix = 128 × 128; 1.7 × 1.7 x 3 mm^3 voxels size; GRAPPA acceleration factor 2) because the study protocol did not include a T2-W image scan besides FLAIR (which is suboptimal for the T1w/T2w calculation since it has a decreased grey-WM contrast due to the inversion pulse (Ganzetti et al., 2014)). Out of 213 participants who completed the intervention, 180 had good quality MRI data at pre- and post-intervention (see, Fig. A.1 for participant flow for the current analyses).

AMC and AZB checked for image quality (see, Fig. A.1 for details). Images were excluded from the analyses if they had motion or ghost artifacts that affected the grey-white matter boundary or image co-registration; 4 subjects were excluded due to brain anatomical concerns that affected image co-registration and could lead to partial volume effects (e.g., ventriculomegaly or asymmetrical ventricles); 8 subjects were excluded due to insufficient brain coverage of their T2-w images for intensity calibration with the MRTool. In addition, visual inspection of the T1-w and T2-w images revealed four participants with confluent white matter lesions beyond what is expected for typical aging, and thus were excluded from the analyses. 33 participants were excluded due to insufficient MRI quality (n=11 active control, n=11 dancing group, n=10 the walking group), resulting in n=43 for the active control, n=51 for dance and n=86 for the combined walking group. The full description of subject flow is detailed in Fig. A.1 and in our previous reports (Baniqued et al., 2018; Ehlers et al., 2017; Voss et al., 2018).

T1w/T2w calculation

We calculated T1w/T2w images with the MRTool registration-segmentation framework in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; (Ganzetti et al., 2014). First, T2-W images in the individual space were co-registered to T1-W images through a 6 degrees of

freedom rigid-body transformation. The effect of the transmit field intensity inhomogeneities (B1 field) differs between T1w and T2w images, and thus the division of the T1-w image by the T2-w image does not automatically cancel for the signal variations due to intensity non-uniformity (INU). Therefore, we corrected for INU using the INU correction algorithm from SPM12 before calculating the ratio. Additionally, because the T1-w and T2-w images have different intensity scales across individuals and scanners, we performed a calibration method to normalize the sensitivity profiles across subjects and scan sessions.

The bias correction algorithm included the default SPM parameters for smoothing (60mm) and regularization (10^{-4}). The regularization algorithm models the intensity variations between images, while the smoothing algorithm uses 60 mm of full-width half-maximum Gaussian smoothness of the intensity bias. The bias field smoothing parameter estimates the level of low-pass filtering (attenuation of high frequency data) applied to the estimated intensity non-uniformity field.

After the INU correction, the images were calibrated to standardize their intensity scales across sessions and participants (Ganzetti et al., 2014). We could not use the recommended external calibration (using the eye and temporal muscle) due to insufficient head coverage of the T2-w images. Instead, we used the internal calibration that rescales the images using the whole brain intensity distribution (Ganzetti et al., 2014; Glasser and van Essen, 2011). This calibration method chooses an internal hallmark inside the brain to standardize (i.e., normalize to a global mean) the intensity values. This is considered less optimal because it may attenuate differences in myelin levels between groups. To address this, we examined the variability in image histograms before and after calibration and across experimental groups, and we observed consistent intensity scales and ranges across groups after the calibration procedure. Fig. A.2

shows histograms of intensity values for T1w and T2w images before and after calibration for 5 random subjects from each intervention group.

Then, the T1w/T2w were calculated in individual space using the bias corrected and calibrated images. Then, images were brain extracted to remove non-brain tissue and transformed to Montreal Neurological Institute (MNI) space $1mm^3$ in SPM (Ganzetti et al., 2014). The T1w/T2w signal shows values ranging from 0 to 2, with values closer to 0 representing CSF, values closer to 1 found in grey matter structures (e.g., caudate nucleus, thalamus), and higher values found in white matter regions (corpus callosum).

White matter hypointensity volume calculation

We calculated white matter lesion load as the total volume of white matter hypointense signal on on T1-w images using FreeSurfer's image analysis suite 5.3 probabilistic procedure (http://surfer.nmr.mgh.harvard.edu/). Freesurfer segments white matter hypointensities using spatial gradients across tissue types (Fischl et al., 2002).The automatic segmentation was examined for errors or grey matter misclassification. For details on the MRI preprocessing of the volumetric data see (Ehlers et al., 2017).

Skeletonization and region selection

We used Tract-Based Spatial Statistics (TBSS) in FSL (Smith et al., 2006) to restrict the analyses to the center of white matter tracks. This was to minimize the effects of possible partial volume due to individual and age differences in anatomy, to focus the analyses on the normal-appearing white matter, and to allow direct comparison with our earlier DTI findings from this sample (Burzynska et al., 2017). We used the non-FA TBSS pipeline for the T1w/T2w images to project them onto the group white matter skeleton with a threshold of fractional anisotropy > 0.2, as we described earlier (Burzynska et al., 2017). To confirm that the T1w/T2w voxels were

correctly projected onto the white matter skeleton, we de-projected all skeletonized T1w/T2w images for visual inspection in subject's native space; the deprojection was accurate for all participants and regions except for regions 3 and 4 of the corpus callosum in 5 participants, which were treated as missing values.

We extracted T1w/T2w regional values for statistical analyses. Total white matter was defined as all voxels on the white matter skeleton. We examined the five subsections of the corpus callosum (CC) (Hofer and Frahm, 2006) given the anterior-to-posterior gradient of CC's vulnerability to aging (Head et al., 2004). Region 1 (CC1) contains the most anterior fibers of the CC, which project to the prefrontal cortex. Region 2 (CC2) projects to the premotor and supplementary control areas. Region 3 (CC3), the posterior mid-body projects to the primary motor cortex. Region 4 (CC4) projects to the primary sensory cortex. The most posterior region (CC5), where callosal parietal, temporal and occipital fibers cross the CC is region 5 (Hofer and Frahm, 2006).

Other white matter regions included the association fibers connecting regions known to be affected by aging: the fornix (FX), the superior longitudinal fasciculus (SLF), the external capsule (EC), the cingulum (CING), and the uncinate fasciculus (UNC). In addition, we included two other major white matter landmarks: the forceps minor (fMIN) and forceps major (fMAJ), containing callosal fibers and thalamic projections to the frontal lobes and the occipital lobes, respectively. The corticospinal tract (CST) represented the major projection from the motor cortex to the lower motor neurons. To define fMIN, fMAJ, UNC, SLF and CST on the white matter skeleton, we used the tract probability maps from the Johns Hopkins University white matter tractography atlas (Hua et al., 2008); http://cmrm.med.jhmi.edu). We thresholded the tract probability maps at 10-15%, depending on a tract, with the aim to maximize the overlap with

white matter skeleton but avoid including voxels from neighboring tracts (Fig. 2.1). For the FX and EC, we used the Johns Hopkins University white matter labels in FSL. Finally, since the prefrontal cortex is vulnerable to aging (Head et al., 2004) and its volume and function has been shown to benefit from greater cardiorespiratory fitness or aerobic exercise (Colcombe and Kramer, 2003; Voss et al., 2013), we defined prefrontal white matter using a cutoff of $y > 12$ in MNI space (Burzynska et al., 2013). To minimize the effects of the outliers but to avoid removing data points, we identified outliers as < 1st percentile or > 99th percentile of distribution (i.e., winsorized) by replacing them with the nearest value in the 1st or 99th percentile. This criterion was applied to mean T1w/T2w data for each region of interest. For each variable and intervention group, no more than 3% values were winsorized.

Finally, we inspected the normality of the T1w/T2w data and found a bimodal distribution in the following regions: fMAJ, UNC, EC and CST. This could have diluted the between-groups mean differences in these regions, leading to underestimation of the intervention effects and overestimation of the effects of time. We excluded these from the main analyses and included them in Table A.1.

Cognitive assessment

Cognitive assessment included the Virginia Cognitive Aging (VCAP) battery (Salthouse, 2009) and two additional experimental executive function tasks (task switching and spatial working memory (Baniqued et al., 2018). As the task switching and spatial working memory tasks load on the reasoning construct of the VCAP (Baniqued et al., 2018; Voss et al., 2018), we grouped them with the matrix reasoning, Shipley abstraction, letter sets, spatial relations, paper folding, and form boards to create an executive function composite (Baniqued et al., 2018; Voss et al., 2018). In addition, the VCAP assessed episodic memory (word recall, paired associates,

logical memory tasks), perceptual speed (digit symbol substitution, letter comparison, pattern comparison), and vocabulary (Wechsler Adult Intelligence Vocabulary, picture vocabulary, and synonym/antonym). We used the vocabulary construct only for sample description, because there is no evidence linking physical activity interventions with gains in crystallized abilities.

We removed outliers (i.e., winsorized) from each cognitive task before calculation of the composite scores at one percent of their distributions, no more than 1% values were winsorized. Then, we expressed both pre and post-intervention individual values as standardized scores (z-scores) using the mean and standard deviation of the pre-intervention distribution. Finally, we calculated composite scores for both pre- and post-intervention as mean z-scores of tasks within each cognitive domain.

Statistical analyses

We used linear mixed-effects models with parameter estimates fitted using the R lme4 package (Bates et al., 2015) to compare change in T1w/T2w between the three groups (walking, dance, and active control). Models included fixed effects of time, group, and the time-by-group interaction as well as random intercepts. The group factor was coded using Helmert contrasts. This allowed us to compare the active control against the average of all the walking and dance groups. Then, to contrast the effects of walking vs active control and dance vs. active control we fitted additional linear mixed-effect models using a contrast matrix with dummy codes for the three groups, such that the active control was the reference. We standardized all quantitative variables, but not factors, to create partially standardized regression coefficients. The standardization of our variables rendered regression coefficients (β) that are loosely interpreted like correlation coefficients in terms of effect size (Ferguson, 2009). We tested the assumptions

of the linear mixed-effects models by visually inspecting the normality of residuals, as well as the distribution of the residuals vs. fitted values.

For correlational analyses, 6-month change scores in the variables of interest were calculated as the post-intervention z-score minus pre-intervention z-score (note that we used the pre mean and standard deviation to transform both pre and post data). We used partial Pearson's correlations in R ppcor to study the associations between change in T1w/T2w and cognition (controlling for age, sex and education), and between change in T1w/T2w and cardiorespiratory fitness (controlling for age and sex) within each intervention group. Because these correlational analyses were exploratory, we corrected for multiple comparisons using the false discovery rate method as implemented by p.adjust (p.value, method="fdr") in R. Statistical significance was accepted at $p<0.05$ for two-tailed tests.

We created figures using the ggplot function in the ggplot2 package (Wickham, 2009) and the multiplot function within the coefplot package (Lander, 2016). All statistical analyses were completed using R version 4.0.1.

2.4. Results

One-way ANOVA showed no baseline differences in age, sex, education, resting blood pressure, cardiorespiratory fitness, regional T1w/T2w values and white matter lesion volume between the active control, walking, and dance groups (Table 2.1), indicating successful randomization. In addition, mean adherence rates were 80% for the active control, 78% for the dancing group and 77% for the walking group, $F= 0.88$, Df = 2, $p=0.41$.

Table 2.1

Baseline characteristics of the sample

Variables	Control n=43	Dance n=51	Walking n=86	*p* value
General characteristics				
Age	66.3±4.5	65.8±4.6	64.8±4.2	0.143
Women, n (%)	26 (65.0)	37 (75.5)	54 (67.5)	0.508
Education, yrs	16.3±3.0	15.3±3.3	15.9±2.6	0.321
MMSE	28.5±1.4	28.4±1.5	28.5±1.4	0.879
BMI	30.4±6.1	30.5±5.9	30.4±4.9	0.993
Systolic BP	132.2±14.9	132.6±12.6	131.9±14.2	0.963
Diastolic BP	79.6±7.9	82.7±17.7	78.5±7.5	0.137
CRF	19.0±4.5	19.5±4.1	20.0±4.5	0.456
Cognition				
Word recall	43.9±8.9	44.6±8.4	43.7±9.0	0.842
Paired associate	0.33±0.2	0.30±0.2	0.36±0.2	0.500
Logical memory	43.6±9.1	45.1±8.2	44.4±8.1	0.684
Digit symbol	62.0±13.0	66.3±15.0	65.8±12.7	0.238
Letter comparison	9.1±1.8	9.6±1.6	9.5±1.7	0.373
Pattern comparison	14.2±2.1	14.8±2.4	15.1±2.6	0.189
Matrix reasoning	8.6±2.9	8.5±3.1	7.6±2.8	0.079
Shipley abstraction	12.5±3.5	12.9±3.5	11.6±3.5	0.097
Letter set	11.3±2.4	11.2±2.7	10.7±2.7	0.373
Spatial relations	8.3±5.1	7.7±5.0	7.9±3.9	0.820
Paper folding	5.1±2.6	5.5±2.6	5.1±2.4	0.532
Formboard	5.6±3.8	5.8±3.5	5.3±3.5	0.810
SPWM	0.79±0.1	0.80±0.1	0.81±0.1	0.677
Task switching RT	296.8±151.0	318.5±183.2	320.5±152.5	0.727
T1w/T2w levels				
Total	1.39±0.1	1.40±0.1	1.39±0.1	0.818
CC1	1.47±0.1	1.48±0.1	1.46±0.1	0.664
CC2	1.36±0.2	1.35±0.2	1.38±0.2	0.572
CC3	1.15±0.3	1.14±0.3	1.19±0.2	0.513
CC4	1.06±0.3	1.06±0.3	1.09±0.3	0.784
CC5	1.48±0.2	1.46±0.2	1.46±0.2	0.812
prefrontal	1.42±0.1	1.43±0.1	1.43±0.1	0.545
fMIN	1.49±0.1	1.49±0.1	1.48±0.1	0.466
Cingulum	1.46±0.1	1.47±0.1	1.47±0.1	0.698
SLF	1.43±0.1	1.45±0.1	1.45±0.1	0.186
FX	0.90±0.1	0.89±0.1	0.91±0.1	0.863
WM hypointensity (mm^3) log	7.54±0.64	7.49±0.66	7.50±0.59	0.915

Note. MMSE= Mini-mental state examination, BMI= body mass index, BP=blood pressure, CRF=cardiorespiratory fitness, SPWM= spatial working memory, RT = reaction time, CC = corpus

callosum, fMIN= forceps minor, SLF = superior longitudinal fasciculus, FX = fornix; WM = white matter.

Intervention effects

We first compared the active control condition to the average effect of the walking and dance conditions. We found significant time-by-intervention interactions in total white matter, the genu and splenium of the corpus callosum, the forceps minor, the cingulum, and the superior longitudinal fasciculus (Table 2.2).

Table 2.2

Time-by-intervention interactions in white matter T1w/T2w

	Walking + Dance vs. Control			Walking vs. Control			Dance vs. Control		
Region	*β*	SE	*p*	*β*	SE	*p*	*β*	SE	*p*
Total	0.26	0.11	**0.02**	0.25	0.11	**0.03**	0.27	0.13	**0.04**
CC1	0.24	0.09	**0.01**	0.22	0.10	**0.02**	0.22	0.11	**0.05**
CC2	0.09	0.06	0.12	0.09	0.06	0.13	0.09	0.06	0.19
CC3	0.05	0.05	0.26	0.06	0.05	0.26	0.05	0.06	0.38
CC4	0.06	0.04	0.13	0.05	0.04	0.25	0.07	0.05	0.25
CC5	0.14	0.06	**0.01**	0.18	0.06	**0.01**	0.10	0.07	0.12
Prefrontal	0.17	0.10	0.10	0.16	0.10	0.14	0.18	0.12	0.14
fMIN	0.14	0.07	**0.03**	0.15	0.07	**0.04**	0.14	0.07	0.20
CING	0.15	0.06	**0.02**	0.16	0.07	**0.02**	0.14	0.02	0.07
SLF	0.15	0.07	**0.05**	0.13	0.07	0.09	0.16	0.09	0.08
FX	0.01	0.05	0.86	0.01	0.05	0.70	-0.03	0.05	0.94

SE= standard errors, CC= corpus callosum, fMIN= forceps minor, CING= cingulum, SLF= superior longitudinal fasciculus, FX= fornix. *β* are standardized. Bold highlights $p<.05$. White matter regions are explained and visualized in Fig. 2.1.

Next, we compared the effects of walking versus active control and the effects of dance versus active control. For the walking versus active control contrast, we found time-by-

intervention interactions in total white matter, the genu and splenium of the corpus callosum, the forceps minor, and cingulum. For the dance versus active control contrast, we found time-by-intervention interactions in total white matter and the genu of the corpus callosum. Using Helmert contrasts, we found no difference in the time-by-intervention interactions between the dance versus walking groups, see Table A.2. In addition, we found that both the walking and dance interventions resulted in an increase in white matter T1w/T2w signal or a reduced rate of decline relative to the active control condition, as shown in Fig. 1. Additional analyses demonstrated that controlling for total white matter lesion volume did not impact the time-by-intervention interaction effect (Table A.3). In addition, there was no overall effect of time on white matter lesion volume (i.e., no significant 6-month change). We also did not find time-by-group interaction effect for white matter lesion as the dependent variable (Table A.4).

Additionally, we replicated results from Burzynska et al. (2017) using DTI-FA, showing significant time-by-intervention interactions in the fornix and forceps minor for the dance vs. control contrast (Table A.4). Lastly, we repeated the linear-mixed effects models using the raw T1w/T2w to demonstrate that removing outliers (i.e., winsorizing) did not have a significant impact on the main results (Table A.5.).

In sum, our results show positive intervention-related changes in the T1w/T2w signal when compared to the active control (Fig. 2.1), with more regions affected in the walking group than in the dance group.

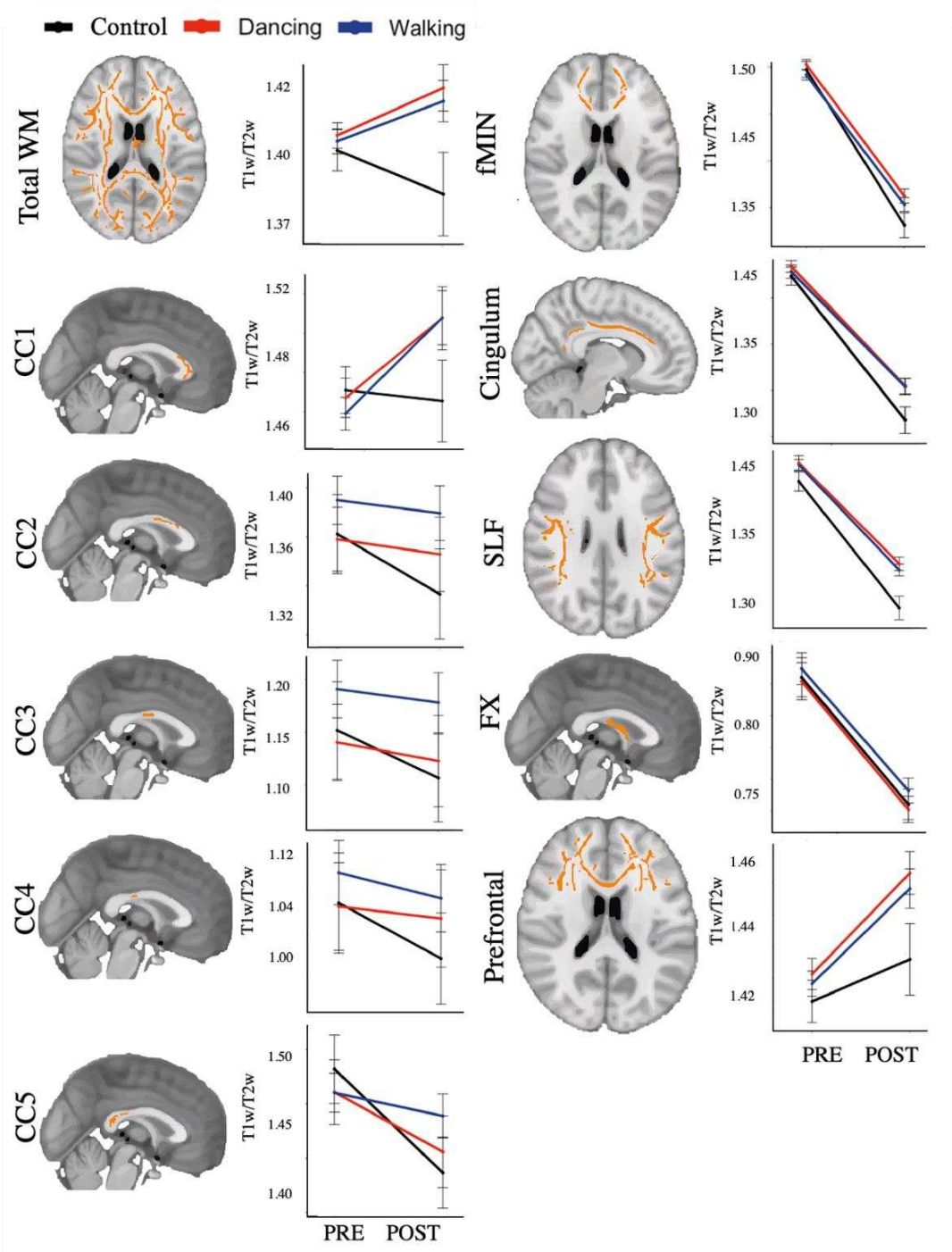

Figure 2.1

6-month change in T1w/T2w signal in the Active Control, Walking and Dance groups. Note. The points represent the group means at both preintervention (PRE) and postintervention (POST) for each intervention group, and error bars represent 95% confidence intervals. WM = white matter; CC = corpus callosum; fMIN = forceps minor; SLF = superior longitudinal fasciculus; FX = fornix.

6-month longitudinal decline in T1w/T2w

We observed a consistent pattern of decline in the T1w/T2w signal over a period of 6 months in the active control group for all white matter regions, except the genu of the corpus callosum and prefrontal white matter. The largest effect sizes were observed in forceps minor and cingulum, where we also observed significant time-by-group interactions. Fig. 2.1, shows the means for the T1w/T2w at preintervention and postintervention for each group, while Fig. 2.2 shows the standardized β-coefficients for all white matter regions for the effect of time in the active control group. Finally, exploratory correlations between changes in T1w/T2w and chronological age group revealed significant associations in the genu, anterior body of the corpus callosum, and the splenium in the active control group (Fig. 2.3).

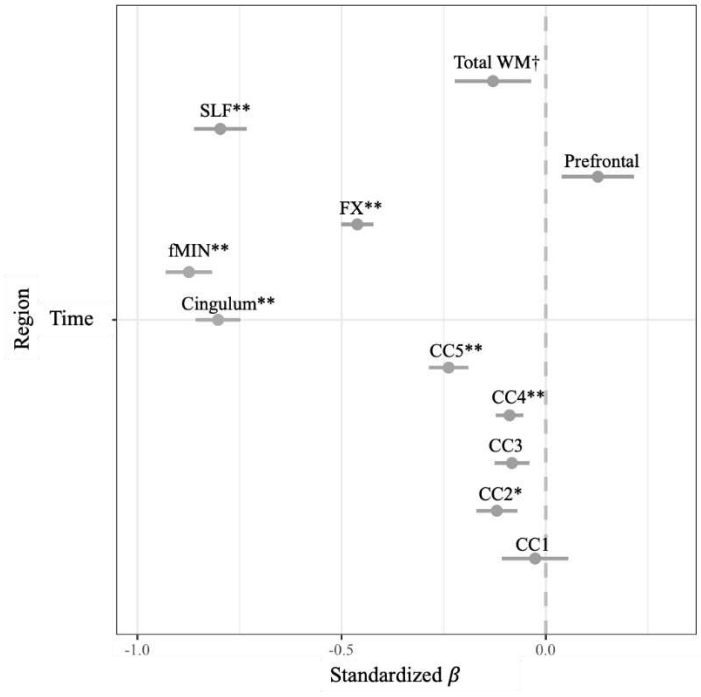

Figure 2.2
*Standardized β coefficients for the fixed effects of time in the active control. Note. Asterisks indicate †p<0.10, *p<0.05, **p<0.01. Error bars represent 95% confidence intervals. WM = white matter; CC = corpus callosum; fMIN = forceps minor; SLF = superior longitudinal fasciculus; FX = fornix.*

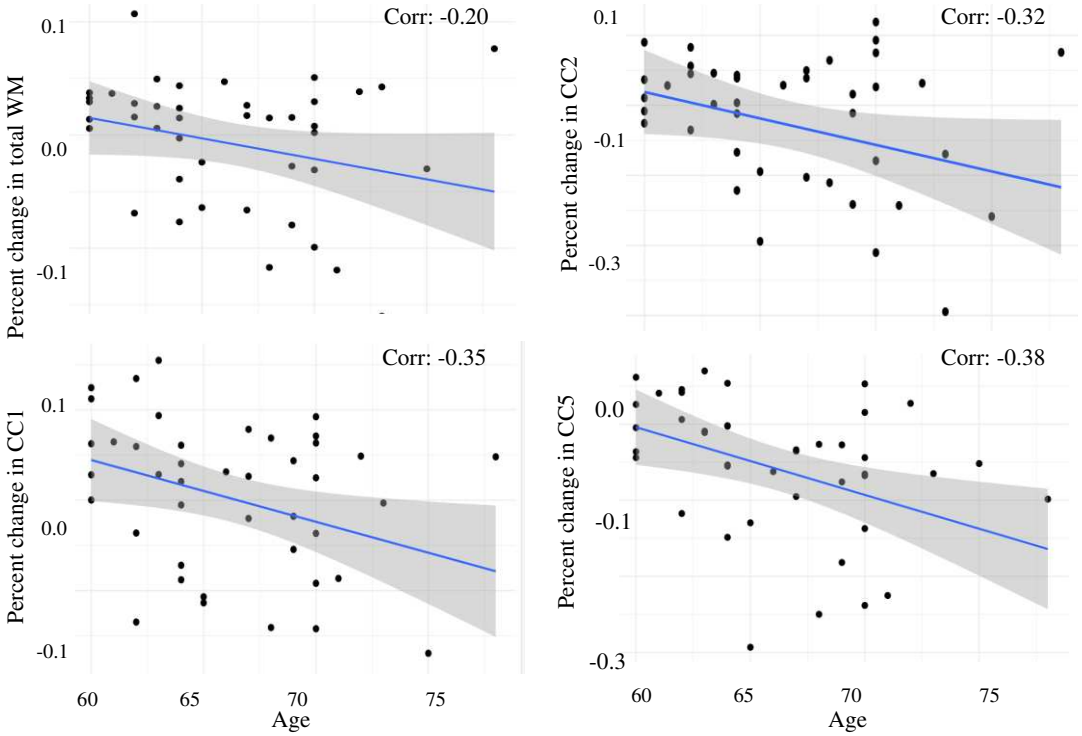

Figure 2.3

Relationship between change in T1w/T2w and age. Note. Scatterplots show the relationship between the percent change in T1w/T2w and age in the active control group. The negative relationship indicates that greater age was associated with a more negative change in white matter T1w/T2w. White matter regions displayed are total white matter (WM), CC1 (genu), CC2 (anterior body), CC5 (splenium). Error shading indicates 95% confidence intervals.

Change in T1w/T2w signal and cognition

We correlated the 6-month change in T1w/T2w in the five regions that showed time-by-intervention interactions in the walking group with change in memory, perceptual speed, and executive function. All analyses controlled for age, sex, and education. A positive change in the T1w/T2w correlated with a positive change in episodic memory in the genu of the corpus callosum and the cingulum (Table 2.3). None of these effects were significant in the active control and dance groups. Lastly, we found no associations between baseline T1w/T2w and baseline cognitive scores (Table A.6).

Table 2.3. Partial correlation coefficients between change in T1w/T2w and change in cognitive scores

	Episodic Memory			Perceptual Speed			Executive Function		
Region	Control	Walking	Dance	Control	Walking	Dance	Control	Walking	Dance
	n=43	n=86	n=51	n=43	n=86	n=51	n=43	n=86	n=51
Total	0.04	0.28*	-0.04	-0.27	-0.06	0.12	-0.34	0.01	-0.04
CC1	-0.12	0.27*	-0.04	-0.21	0.10	0.09	0.10	0.10	0.10
CC5	-0.25	0.16	-0.20	-0.04	0.17	0.03	0.17	0.17	0.17
fMIN	0.01	0.21	0.06	-0.27	0.01	0.08	0.01	0.01	0.01
CING	-0.09	0.21	0.01	-0.24	-0.07	0.10	-0.07	-0.07	-0.07

*p<0.05. CC= corpus callosum, fMIN= forceps minor, CING= cingulum. Partial correlations between change in T1w/T2w and cognition within each intervention group, controlling for age, sex, and education. Significance corrected for false discovery rate.

Change in T1w/T2w signal and cardiorespiratory fitness

We examined whether intervention-related changes in T1w/T2w were associated with increased cardiorespiratory fitness. Pearson partial correlations, controlling for age and sex, revealed no significant associations between change in T1w/T2w and cardiorespiratory fitness (Table 2.4).

Table 2.4. Partial correlation coefficients between change in T1w/T2w and change in cardiorespiratory fitness

Region	All	Control	Walking	Dance
	n=180	n=43	n=86	n=51
Total	-0.05	-0.05	-0.02	-0.05
CC1	-0.08	-0.09	-0.08	-0.04
CC5	-0.10	-0.10	-0.03	-0.18
fMIN	-0.06	-0.08	-0.02	0.02
Cingulum	-0.06	-0.09	-0.01	-0.03

CC= corpus callosum, fMIN= forceps minor, CING= cingulum. Partial correlation coefficients between change in T1w/T2w and cardiorespiratory fitness within each intervention group, controlling for age and sex.

2.5. Discussion

Results from our RCT revealed positive changes in the standardized T1w/T2w in the aerobic exercise groups, providing preliminary evidence for experience-induced plasticity in the aging white matter. These changes were observed in several late-myelinating white matter regions in the walking and dance groups as compared to a decline in the active control group. In the active control group, the T1w/T2w signal showed widespread within-person decline, and this decline was pronounced with advancing age. Importantly, longitudinal analyses showed that controlling for total white matter lesion volume did not impact the intervention effect. Finally, the change in T1w/T2w in the walking group correlated with a positive change in episodic memory. However, change in T1w/T2w was not associated with cardiorespiratory fitness.

Aerobic exercise training increased T1w/T2w in the adult white matter

As predicted, aerobic walking training resulted in an increase in the white matter T1w/T2w signal, relative to an active control condition which included flexibility, strength, and balance exercises. Thus, our findings are in alignment with the previous cross-sectional and intervention studies showing a positive relationship between aerobic exercise, grey matter structure, and functional activity (Colcombe et al., 2006; Erickson et al., 2011; Voss et al., 2010). Together, these findings are the first from a RCT showing exercise-related plasticity on white matter (Burzynska et al., 2017; Clark et al., 2019; Voss et al., 2013).

Interestingly, although the effects of the aerobic walking on the T1w/T2w signal were significant for the mean of all white matter voxels, regional analyses suggested that results were specific to the late-myelinating regions containing association and commisural fibers: the genu and splenium of the corpus callosum, forceps minor, and the cingulum (Lebel et al., 2019). This is consistent with earlier correlational studies that found positive correlations between aerobic

exercise and fractional anisotropy in the body and genu of the corpus callosum (Loprinzi et al., 2020), and in the cingulum bundle (Marks et al., 2011) in healthy older adults. Because white matter regions that myelinate later in development are thought to deteriorate earlier with age (Brickman et al., 2012), our findings suggest that regions vulnerable to aging retain some level of plasticity that can be induced by aerobic exercise.

However, we found no associations between increased cardiorespiratory fitness and change in T1w/T2w signal; this is in contrast to earlier clinical trials reporting such correlations with brain functional activity (Voss et al., 2018), grey matter volume (Kramer and Colcombe, 2018), and fractional anisotropy (Burzynska et al., 2014). A possible explanation is that cardiorespiratory fitness is a multi-component measure that comprises oxygen supply (e.g., cardiac output, erythrocyte mass, vascular resistance) and demand factors (e.g., muscle mitochondrial respiration rate) (Lundby et al., 2017). Thus, changes in the T1w/T2w signal may be associated with some of these physiological adaptations to exercise, which we did not measure. It is also possible that such associations are no longer present at 6 months of training since cardiorespiratory fitness improvements taper off at 3-12 months of training, after the initial rapid increase (Erickson et al., 2011; Lundby et al., 2017; Vidoni et al., 2015; Voss et al., 2018). To identify the physiological mechanisms linking aerobic exercise to increases of T1w/T2w signal, future studies should include measures of physiological and vascular adaptations associated with cardiorespiratory fitness, such as changes in neurotrophic factors, markers of vascular function and inflammation, as well as skeletal muscle metabolism (Tari et al., 2019).

Is walking more effective than dancing in increasing T1w/T2w?

Although we observed no significant differences in T1w/T2w signal change between the dance and walking conditions, the descriptive effect sizes observed hint at a possible advantage

of walking. Possible explanations include the smaller sample size of the dancing (n =51) compared to the walking group (n=86) or the lower volume and intensity of the dance training compared to the aerobic walking. For example, the dance classes included a significant amount of low-intensity instructional time, which may explain lower gains in cardiorespiratory fitness in the dance group, as reported by Voss et al. (2018), where only the walking interventions led to gains in cardiorespiratory fitness relative to the active control.

Since the dance training required learning complex perceptual-motor sequences, we expected that this intervention would result in plasticity in additional white matter regions (e.g., the fornix) when compared to the walking training, as reported in (Burzynska et al., 2017) and Table A.4. It is possible that DTI is more sensitive to dance-induced changes in the fornix microstructure than the T1w/T2w signal, since about 40% of its fibers are unmyelinated (Peters et al., 2010). Together, our data suggest that dance and walking interventions may elicit spatially overlapping effects, possibly due to the shared aerobic exercise component.

White matter signal declined over time

T1w/T2w signal decreased over a 6-month period in the majority of white matter regions in the active control group, consistent with earlier findings of a widespread decline in fractional anisotropy that involved association, commisural, and limbic fibers (Bender et al., 2016; Burzynska et al., 2017; Sexton et al., 2014). However, we did not observe 6-month decline in T1w/T2w signal in the genu of the corpus callosum, a late-myelinating tract susceptible to age-related changes according to the development-to-degeneration or anterior-to-posterior gradient hypotheses of brain aging (Brickman et al., 2012; Head et al., 2004). Instead, we found significant 6-month changes in the more posterior sections of the corpus callosum: the body and the splenium. The discrepancy between T1w/T2w and DTI in detecting short-term changes may

be related to different sensitivities of these methods. For example, fractional anisotropy is thought to be particularily sensitive to changes in regions with smaller diameter axons that are coherently oriented and densely packed (e.g., genu, fornix) (Burzynska et al., 2017, 2010). Conversely, the T1w/T2w signal may be better suited to detect longitudinal changes in regions with larger axonal diameter, such as the body and the splenium of the corpus callosum (Lamantia and Rakic, 1990), or in tracts containing more fiber crossings such as the cingulum bundle or the superior longitudinal fasciculi (Glenn et al., 2016). Lastly, we observed that the magnitude of decline of T1w/T2w signal within the corpus callosum was greater with advancing age in the active control group, consistent with earlier DTI findings (Fanning et al., 2017). However, the observation that the T1w/T2w changes with age is supported by studies using relaxometric measurements, where the amplitude of the T1 and T2 relaxation intensity values for the white matter changes as a function of age; with the highest peaks in the white matter observed after the age of 60 (Saito et al., 2009). This increase is thought to reflect brain demyelination, edema or inflammation (Deoni, 2010). Similarly, R1, a measure of longitudinal relaxation rate, shows consistent decline after the age of 70, possibly reflecting the rate of white matter degeneration and proliferation of glia (Yeatman et al., 2014). In sum, our results suggest that T1w/T2w signal can detect short-term age-related changes in the white matter.

Increases in white matter signal correlated with improved episodic memory

In the walking group, we found a positive association between changes in episodic memory and T1w/T2w in the total white matter, the genu of the corpus callosum and, at trend level, in the cingulum. The genu of the corpus callosum is known to be involved in interhemispheric integration and the recruitment of the ventrolateral prefrontal cortex in episodic memory processes in older adults (Bucur et al., 2008). Decreased fractional anisotropy in the

dorsal cingulum has been linked to episodic memory impairment (Lockhart et al., 2012). Thus, our findings in humans complement studies in rodents showing activity-dependent myelin formation linked to improved memory performance (Fields and Bukalo, 2020). In particular, a recent study in mice demonstrated that new myelin formation is required for proper functioning of prefrontal regions and consolidation and retrieval of remote fear memories (Pan et al., 2020).

Our findings also agree with an earlier study that observed a correlation between increased gray matter volume in the prefrontal and cingulate cortices and improvement in episodic memory performance, independent of aerobic fitness measured with a lactate step test (Ruscheweyh et al., 2011). Overall, our results suggest that white matter plasticity measured as change in T1w/T2w signal is relevant for episodic memory processes, but this change in T1w/T2w was not associated with cardiorespiratory fitness gains.

Given the known effects of aerobic exercise on executive functions and processing speed (Colcombe and Kramer, 2003; Kramer and Colcombe, 2018), and the reliance of processing speed on white matter integrity (Chopra et al., 2018), we were surprised to find no associations between change in T1w/T2w and change in these two cognitive abilities. Future studies need to determine whether exercise-induced gains are specific to memory function, using a broader array of cognitive assessments as well as measures like brain-derived neurotrophic factor (Erickson et al., 2011).

T1w/T2w as a measure of white matter plasticity

Because this is the first application using T1w/T2w to study white matter plasticity, our findings need to be interpreted with caution. Despite recent animal studies showing activity-dependent remodeling of myelin and axons as important mechanisms of neuroplasticity (Bobinski et al., 2011; Chen et al., 2019; Fields and Bukalo, 2020), it is still premature to relate

changes in T1w/T2w to any particular microstructural mechanism. For example, T1w/T2w signal was initially used to map myelin content and showed a strong correlation with myeloarchitecture of the developing neocortex in humans and primates (Glasser and van Essen, 2011). Subsequently, T1w/T2w was shown to correlate with oligodendrocyte-specific gene expression in humans (Patel et al., 2020) and MRI-derived synthetic myelin volume fraction in human white matter (Saccenti et al., 2020). However, other studies have reported correlations of T1w/T2w signal with MRI estimates of axonal diameter (Arshad et al., 2017), axonal density (Fukutomi et al., 2018), iron content (Shams et al., 2019), as well as weak correlations between T1w/T2w and myelin water fraction in subcortical structures (Uddin et al., 2018). This is consistent with the fact that T1 and T2 relaxations are determined by biophysical properties that may be altered by several histological processes in the white matter tissue (Deoni, 2010), limiting T1w/T2w specificity. Also, T1 and T2 relaxations are not independent, namely, recovery of longitudinal T1 magnetization co-occurs with the loss of T2 transverse magnetization (Deoni, 2010). However, our results in combination with the high validity of the T1w/T2w signal after calibration (Arshad et al., 2017) suggest that the T1w/T2w offers a promising measure of white matter microstructure, independent of the tissue diffusivity properties. Therefore, although our results suggest that the T1w/T2w offers a promising measure of WM microstructure, further examination, using more accurate estimates of myelin and axonal density (Lee et al., 2020; MacKay and Laule, 2016), is required.

Exercise intervention and white matter lesions

Given the prevalence of white matter lesions in the aging population, and their predictive role in cognitive impairment and Alzheimer's Disease (Yoshita et al., 2006) it is important to consider white matter lesions as both the target and a confounding factor in exercise

interventions. In line with most longitudinal studies, we found no intervention-induced change in white matter lesion load (Torres et al., 2015). This may be explained by the short duration of our intervention, considering that healthy individuals with minimal small vessel disease show slower progression rates of white matter lesions when compared to cognitively healthy individuals with higher cardiovascular burden or Alzheimer's Disease patients (Ramirez et al., 2016). Similarly, a recent RCT studying the progression of white matter hyperintensities failed to find an effect of 24-month of moderate-intensity physical activity (Venkatraman et al., 2020a). In contrast, longer longitudinal cohort studies have found small but significant associations between physical activity and reduced periventricular and deep white matter hyperintensities in cognitively healthy individuals after 5 years (Podewils et al., 2007) and 3-year follow-up (Gow et al., 2012).

Finally, to further account for the potential effect of white matter lesions in the T1w/T2w analyses, we used Tract-Based Spatial Statistics, a method that searches for the highest fractional anisotropy value perpendicular to the white matter tract, which should exclude voxels with typically low anisotropy within the white matter lesions. However, as shown in Fig. A.3., some voxels from white matter lesions might have been included in the analyses in a few subjects with more confluent posterior periventricular lesions. However, we expect that this effect would be localized to certain regions and present in only a few participants and, thus, have little effect on T1w/T2w signal in the total white matter. This is supported by the fact that we found no effect of total white matter lesion volume on the treatment effect. However, focusing the analyses on tract centers or normal appearing white matter might have underestimated the effects of intervention (Sexton et al., 2016), as aerobic exercise could improve vascular risk factors associated with white matter signal abnormalities.

Limitations and future directions

We measured cardiorespiratory fitness as the main physiological variable to be manipulated by the aerobic exercise intervention. However, our results suggest that other measures need to be considered to understand white matter plasticity, such as neurotrophic factors as well as markers of inflammation and vascular function. Furthermore, we did not collect a measure of performance gain in the dance group, which limits our interpretation of the effects of dance training on the white matter. Another potential limitation is that the observed effect sizes can be seemingly small, but we believe these can be larger with longer longitudinal designs (>6 months) and more representative samples. For example, Erickson et al. (2011) reports medium to large effect sizes when studying exercise-induced changes in the hippocampus volume, with larger effect sizes observed in the anterior hippocampus. However, this change in hippocampal volume was studied in the context of a 12-month intervention and the effects were half at 6-months, comparable to those obtained in our study. In addition, our sample was composed of healthy older adults with few comorbidities, mostly normotensive (mean blood pressure of 132/69 mmHg), and highly educated (16 mean years of education) which could have diminished the intervention-induced effects observed. Lastly, although we used a false discovery rate correction for our exploratory analyses, our primary linear-mixed effect analyses were not corrected. Therefore, a replication of these findings is necessary. These intervention-induced plasticity effects need to be tested in larger and more diverse longitudinal and experimental studies. Thus, we provide effect size estimates to help guide sample size consideration in future clinical trials.

Next, because our T2-weighted images had limited brain coverage, we were not able to include other WM regions of the hippocampal formation that may be key for episodic memory processes (Burgess et al., 2002), fronto-temporal connections such as uncinate fasciculus, or lower sections of the corticospinal tract (i.e., cerebral peduncles). Future studies should include

these white matter regions to further understand the effects of walking and dance training on the aging white matter and identify new associations between change in T1w/T2w signal with episodic memory, processing speed, and executive function. Another potential limitation is using *b*=0 images from DTI acquisition as T2-w images for T1w/T2w calculation, as b0 images are subjected to echo planar imaging distortions, in addition to potential non-linear signal intensity variations due to the GRAPPA reconstruction. However, given that we used a small acceleration factor of 2, the typical posterior-to-anterior signal intensity variations due to GRAPPA were negligible in our images (Robson et al., 2008). However, because of these pulse sequence differences, the results from this study need to be replicated in other T1w/T2w studies using longer echo trains with lower flip angle pulses. In addition, future studies should consider evaluating the differences in performance of distinct processing workflows for the T1w/T2w signal (e.g., varying INU algorithms, and the effects of possible regional differences in SNR), especially with the development of high-field MR scanners, where the INU correction becomes increasingly important (Uwano et al., 2014).

Finally, Tract-Based Spatial Statistics analysis focuses on normal appearing white matter and the centers of the tracts. We carefully examined the projection of voxels onto the skeleton to ensure that the voxels were sampled consistently across and within subjects. We believe this more rigorous approach provides more confidence in our results, as it helps to avoid partial volume effects with cerebrospinal fluid or grey matter, which are likely to occur in older samples with heterogenous brain anatomy due to age-related atrophy (Scahill et al., 2003).

2.6. Conclusion

Our study provides evidence for white matter plasticity in older adults induced by aerobic walking and dance, measured as an increase in T1w/T2w signal. The findings suggest that the

white matter in the adult brain retains plasticity in vulnerable regions and that these changes can be observed on a short-term scale. Further studies are needed to understand the exercise-induced adaptations that lead to increased T1w/T2w and that mediate effects on episodic memory function. Given that myelin-sensitive imaging MRI is often not collected within the large studies on aging (e.g. ADNI (Jack et al., 2008), UK Biobank (Alfaro-Almagro et al., 2018), ENIGMA (Thompson et al., 2014), HCP (Sotiropoulos et al., 2013)) or randomized controlled trials (e.g. IGNITE (Erickson et al., 2019)), our findings suggest that T1w/T2w may offer an alternative and accessible metric of white matter integrity. Our results encourage revisiting existing datasets to further explore the potential of T1w/T2w to detect white matter decline or plasticity.

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CHAPTER 3

WITHIN-PERSON CHANGES IN THE AGING WHITE MATTER MICROSTRUCTURE AND THEIR MODIFIERS: A META-ANALYSIS AND SYSTEMATIC REVIEW OF LONGITUDINAL DIFFUSION TENSOR IMAGING STUDIES

3.1. Overview

For decades, the adult white matter (WM) has been perceived as "passive" in brain function (i.e., only relaying electrical signals) and "static" (i.e., not capable of or involved in neuroplasticity). As a result, WM function and its potential for change in humans have received less attention than, for example, functional brain connectivity. However, recent evidence from rodent studies shows that the adult WM undergoes short-term structural changes that play a key role in cognitive and motor learning. Despite this, *in vivo* evidence of within-person longitudinal changes and experience-induced plasticity in the adult human WM remains uncertain. Thus, this combined systematic review and meta-analysis synthesized the findings of 30 diffusion tensor imaging (DTI) studies in healthy adults conducted over the past decade to address several questions related to within-person changes in adult WM. The meta-analysis found significant within-person decline in fractional anisotropy (FA) in the whole WM and the genu of the corpus callosum. Older age, longer follow-up times and female sex were associated with greater decline in WM microstructure. The review revealed a consistent pattern of decreased FA and increased mean diffusivity and radial diffusivity in healthy older adults over time. Most studies displayed a regional pattern of WM decline consistent with current theories of WM deterioration (e.g., development-to-degeneration). Our review provided mixed evidence for the effect of modifiers (e.g., exercise) of within-person changes in WM microstructure. Due to high heterogeneity between studies, recommendations for future research are provided. Identifying individual

differences in WM microstructure changes could be critical for identifying the risk or preclinical stages of dementia and opening new opportunities for early interventions, particularly given the lack of effective treatments for cognitive impairment targeting grey matter pathology.

3.2. Introduction

Human white matter (WM) contains mostly myelinated axons, whose properties determine the speed and synchrony in the brain's transduction and transmission of neural signals (Chorghay et al., 2018). WM also contains glia (oligodendrocytes, astrocytes, and microglia) and vasculature that support WM's function, metabolism, and immune processes. The WM of the brain is particularly sensitive to metabolic, inflammatory, and vascular dysfunction (Levit et al., 2020; Mendelow, 2015), all hallmarks of brain aging, Alzheimer's disease, and related dementias. The vulnerability of WM is mainly due to the metabolically-demanding processes of myelin maintenance and long-distance axonal transport (Bartzokis, 2004; Nave, 2010), which are necessary for efficient action potential conduction and metabolic support of myelinated axons (Morrison et al., 2013).

Postmortem studies in healthy older adults have shown that aging is associated with demyelination and decreases in axonal density or diameter (Marner et al., 2003; Mason et al., 2001; Peters, 2002; Tse & Herrup, 2017). Similarly, failed myelin repair (Bartzokis, 2004, 2011) and defects in axonal structure and transportation (Stokin et al., 2005) have been observed in the early stages of Alzheimer's disease, suggesting that grey matter pathology may be triggered or preceded by WM pathology. Specifically, the "myelin" hypothesis of Alzheimer's Disease posits that proteinaceous deposits such as amyloid-β aggregates and tau tangles are the by-products of homeostatic myelin repair processes and disruptions to axonal transport (Bartzokis, 2011). Together, alterations in WM microstructure in both healthy aging and neurodegenerative

processes result in a structural "disconnection" of distributed neural networks, considered one of the primary mechanisms underlying cognitive decline in healthy aging, Alzheimer's disease, and related dementias (Bartzokis, 2004; Nasrabady et al., 2018). However, postmortem histopathological examinations provide no insights into how these changes in WM occur over time and to what extent the magnitude or patterns of within-person progression differs between healthy and pathological aging. Therefore, this article aims to synthesize the evidence from longitudinal *in vivo* studies on the magnitude, direction, spatial patterns, and possible modifiers of naturally occurring within-person changes in adult WM microstructure, measured with diffusion tensor Magnetic Resonance Imaging (MRI). Specifically, we aimed to address the following questions: (1) What is the magnitude and direction of within-person changes in adult WM microstructure? (2) Do within-person changes in white matter microstructure accelerate with age and is there a tipping point? (3) Is there regional variability in WM changes? (4) What factors modify within-person changes in the WM? (5) What are the time periods over which WM microstructural decline can be detected in healthy adults using Magnetic Resonance Imaging?

To date, WM microstructure in aging, Alzheimer's Disease, and related dementias has been studied almost solely using diffusion MRI and predominantly using diffusion tensor imaging (DTI) (Harrison et al., 2020; Madden et al., 2012). DTI provides a voxel-wise estimation of the magnitude and directionality of water diffusion. Fractional anisotropy (FA) measures the directional dependence of diffusion, reflecting fiber-orientational coherence within a voxel. Radial diffusivity (RD) and axial diffusivity (AD) represent diffusivity perpendicular and parallel to the main fiber direction, respectively. Finally, mean diffusivity (MD) reflects the overall magnitude of total water diffusion within a voxel (Beaulieu, 2002). The magnitude of diffusion is determined by microstructural elements that may hinder diffusion in any direction,

such as density, permeability, and integrity of axonal and myelin membranes, activation of glia, microvasculature, and enlargement or tortuosity of extracellular spaces (Jones et al., 2013). This review focuses on the most widely used MRI technique – DTI – although we acknowledge that several more advanced diffusion acquisition and modeling methods have been applied in recent cross-sectional studies.

The study's first aim was to determine the magnitude and direction of within-person changes in DTI parameters in the adult WM microstructure in older age. Age-comparative (cross-sectional) studies on aging consistently report decreased FA, increased MD, RD, and bidirectional age differences in AD (Burzynska et al., 2010). These age differences have been attributed to loss of "WM integrity", including loss of myelin and axons (Madden et al., 2012). Furthermore, cross-sectional studies have suggested nonlinear trajectories in diffusion parameters across the lifespan, suggesting protracted development or myelination until middle adulthood. Specifically, FA has been shown to peak between 20 and 42 years of age, followed by a decline, whereas MD shows a minimum at 18–41 years, followed by a steady increase from middle adulthood onwards (Lebel et al., 2012). An analysis of different diffusion parameters in 3,513 generally healthy people aged 45–77 years from the UK Biobank revealed predominantly nonlinear associations with age (Cox et al., 2016). Specifically, an increase in MD and a decrease in FA accelerated typically after age 60 (Cox et al., 2016). Therefore, our central hypothesis was that within-person changes in middle and older age would predominantly involve declines in FA and increases in MD and RD. In addition, we expected these changes to accelerate after the age of 60.

Our second question addressed the spatial gradients of WM aging. Cross-sectional findings revealed that WM tracts differ in their susceptibility to aging. As a result, several

spatiotemporal gradients have been proposed to explain this selective vulnerability. The overarching model, called development-to-degeneration, retrogenesis, or last-in-first-out hypothesis, posits that WM regions that myelinate later in development deteriorate earlier with age, possibly due to greater metabolic demands on late-differentiating oligodendrocytes (Bartzokis, 2004; Bartzokis et al., 2004). DTI data has lent substantial support for the retrogenesis hypothesis (Brickman et al., 2012), as reflected by studies showing steeper age decline in prefrontal regions and association fibers than in projection fibers (Barrick et al., 2010; Burzynska et al., 2010) and steeper age decline in the most anterior sections of the corpus callosum (Bartzokis, 2004; Head et al., 2004; Salat et al., 2005; Sullivan et al., 2010). Therefore, we hypothesized that late-myelinating WM regions, such as the genu of the corpus callosum, will show a decline in FA and an increase in RD, possibly reflecting demyelination. In contrast, we expected early-myelinating regions, such as the corticospinal tract, to show a plateau or only delayed decline in later life (i.e., after age 70).

Third, we considered the role of various modifiers of within-person changes in adult WM. We expected chronological age to be the main moderator of declines in WM integrity, with older age correlating with a greater magnitude of decline. Furthermore, given the role of sex hormones in promoting myelination, oligodendrocyte proliferation (Ghoumari et al., 2020; Jure et al., 2019; Mendell & MacLusky, 2018), and modulating brain inflammation (Yilmaz et al., 2019), we believe there could be sex differences in age-related declines in WM. So far, cross-sectional DTI studies have reported greater FA in men (Kochunov et al., 2012; Lebel et al., 2012; Ritchie et al., 2018) or no sex differences across the adult lifespan (Kennedy & Raz, 2009). Thus, our analyses concerning sex differences remain exploratory. Other candidate modifiers of WM aging include hypertension (van Dijk et al., 2004), habitual physical activity (Burzynska et

al., 2014; Sexton et al., 2016), or APOE genotype (Sudre et al., 2017). In addition, since people with mild cognitive impairment, subjective cognitive impairment and risk of Alzheimer's Disease show higher MD and lower FA compared to healthy older adults (Brueggen et al., 2019), we will also discuss evidence of within-person change in these groups.

Studying within-person changes in adult WM is important given that for decades, WM has been thought to play a passive role in brain function by merely relaying electrical signals between grey matter regions, where information processing occurs. In addition, the adult WM has been considered "static" after reaching maturity, namely, not capable of or involved in neuroplasticity and only prone to deterioration due to age or disease. Recently, rodent studies have shown that cognitive, and motor learning in adult animals requires myelin plasticity (Gibson et al., 2014; Hines et al., 2015; Jeffries et al., 2016; McKenzie et al., 2014; Sampaio-Baptista et al., 2013). However, because the evidence of training-induced changes in adult human WM microstructure is scarce and inconsistent, WM remains rarely considered the primary target for treatments and interventions against cognitive decline (Mendez Colmenares et al., 2021; Sampaio-Baptista & Johansen-Berg, 2017), which is a missed opportunity. We argue that understanding the naturally occurring within-person changes in WM in older age will lay the foundation for studying adult WM's plastic and regenerative potential in future clinical trials. In in this literature review, we also reviewed evidence from clinical studies to assess the malleability of adult WM microstructure with experience, identify the most promising interventions for inducing change, and determine if there is an age limit to WM plasticity.

Taken together, our overarching hypothesis was that WM microstructure undergoes significant within-person changes during adulthood and aging, and that these changes can be captured noninvasively with DTI. We hypothesized that within-person changes in WM

microstructure in older age: (a) involve predominantly declines in FA and increases in MD and RD; (b) the magnitude of within-person change increases with advancing age; (c) follow the development-to-degeneration spatiotemporal pattern, with greater magnitude of change in late-myelinating regions; (d) are moderated by sex, hypertension, lifestyle factors, and genetic polymorphisms; and (e) people with mild cognitive impairment or risk of Alzheimer's disease show greater magnitude of decline. To answer these questions, we conducted a comprehensive qualitative review of longitudinal DTI studies and performed a meta-analysis on a subsample of studies that provided sufficient data.

3.3. Methods

Our study was pre-registered in the PROSPERO database as PROSPERO 2021 CRD42021273127.

Search Strategy

A systematic search was performed in electronic databases Web of Science and Pubmed up to July 13, 2021. The main search strategy was based on three key components: longitudinal studies, white matter, diffusion tensor MRI, and healthy adult samples. The PubMed database was searched for the terms in either the title or abstract, whereas the Web of Science database was searched for the terms in "topic", which includes title, abstract, and keywords. We searched for studies in peer-reviewed journals, applying no limitations on publication year or language. Given that researchers use different terms to refer to DTI and may not use the DTI or MRI abbreviations in the abstract or title, we used the broad term "diffusion" in our search query. The PubMed query ("white matter"[Title/Abstract] AND "longitudinal"[Title/Abstract] AND "diffusion"[Title/Abstract] AND "adults"[Title/Abstract]) resulted in 283 hits. The Web of Science query ("white matter"(Topic) and longitudinal (Topic) and diffusion (Topic) AND

"adults"(Topic) resulted in 531 hits. After inspection of the results, we noticed that many hits for “longitudinal” were associated with the longitudinal fasciculus. Therefore, we added NOT “longitudinal fasciculus” term to both queries, resulting in 126 hits in PubMed and 248 hits for the Web of Science. In addition, reference lists of included studies and relevant reviews were manually searched for additional eligible studies.

Study selection

ACM and AZB independently screened the title, abstracts, and, where appropriate, full text of identified citations and any disagreements were resolved by consensus. For studies to be included in the systematic review, the following criteria had to be met:

1. Reported DTI parameters (FA, MD, RD, AD) from WM regions collected on at least two occasions per participant. Studies assessing change in only macroscopic measures of WM health (e.g., WM volume or hyperintensity burden) were not included. Both observational longitudinal and clinical trials were considered, but only if they included younger adults AND middle-aged or older adults (i.e., clinical trials in only student/young adult populations (e.g., age 18-25) were excluded). Studies evaluating solely intra- or inter-scanner stability were also excluded. Studies not reporting DTI metrics (i.e., studies reporting only structural connectivity measures) were excluded.
2. Published as an original empirical peer-reviewed journal article. While this may raise susceptibility to publication bias, restricting the search to published results serves as a way to encourage high quality in the included reports. Meta-analyses or review articles on related topics were excluded.
3. Included adult samples of age 18+. Studies including only children and adolescents were excluded.

4. Included cognitively and neurologically healthy adults. Animal and patient populations (e.g., schizophrenia, autism, stroke, concussion, substance abuse, pre-hypertension) were excluded, except for studies involving people with mild cognitive impairment, Alzheimer's disease, and related dementias in older age groups, which were included in the qualitative review.

5. We excluded studies that did not report change (or effect of time) in DTI parameters as a study outcome. These studies included (Fissler et al., 2017; Fletcher et al., 2013; Lampit et al., 2015; Racine et al., 2019), who reported only differences in change between clinical and healthy populations, or (Maltais et al., 2020; Raffin et al., 2021; Scott et al., 2017; Staffaroni et al., 2019) who used change in DTI only as a correlate of change in cognition, brain perfusion, or baseline physical activity. However, we listed these studies in the qualitative review of modifiers of WM change.

6. In addition, we excluded two studies with short follow-up times (<4 weeks) (Chen et al., 2020; Nilsson et al., 2021)

Data selection

The PRISMA flowchart provides an overview of the number of articles screened, included, and excluded (see Fig. 3.1). We included a total of thirty studies in the systematic review, of which half had sufficient data to be included in the meta-analysis. Missing outcomes were requested by contacting the corresponding authors. We contacted 25 authors with insufficient data in the original publication to calculate standardized mean differences or standard errors and received 13 responses.

Given the variability in reporting all four DTI parameters, we focused only on FA to maximize the number of studies for the meta-analyses. At the same time, other DTI metrics are discussed in the qualitative review.

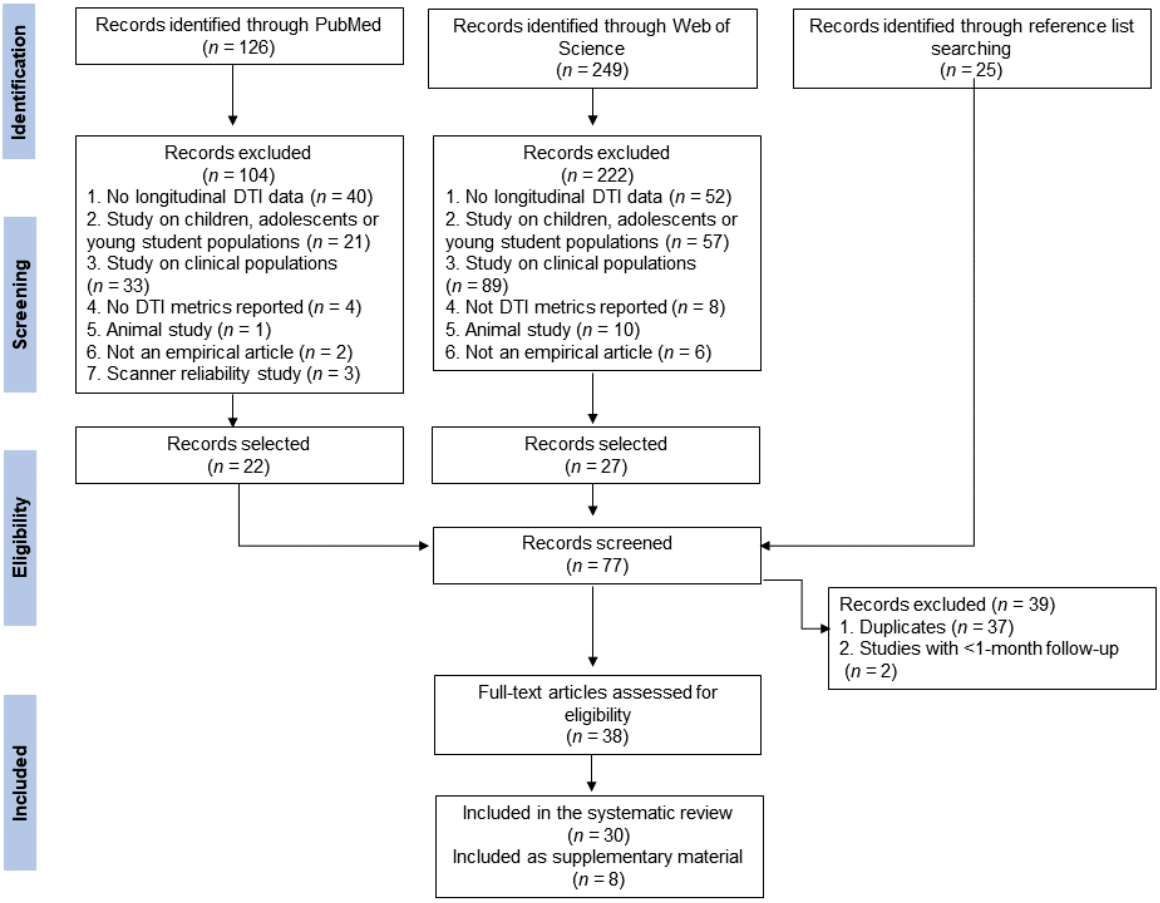


Figure 3.1

Flow chart of selected studies.

From the thirty studies included in the review, the median year of publication was 2015 (range 2009–2021). The median sample size was 56, varying from 11 to 2,125. The average baseline age was 65.3 years (range 18–103 years). The mean follow-up time was 27.7 months (range 2-58 months) (Figure 3.2).

Studies with overlapping samples were excluded when the same aspect of WM structure was examined in both papers (Kocevska, Cremers, et al., 2019; Kocevska, Tiemeier, et al.,

2019). In this case, the study with the largest sample size was first given preference. One study reported multiple follow-up visits (Bender, Völkle, et al., 2016). In this case, for the meta-analysis, we used data from the longest follow-up time. We included six randomized controlled trials with longitudinal DTI data and collected information from the healthy control groups (Burzynska et al., 2017; Cao et al., 2016; de Lange et al., 2017; Engvig et al., 2012; Lövdén et al., 2010; Voss et al., 2013).

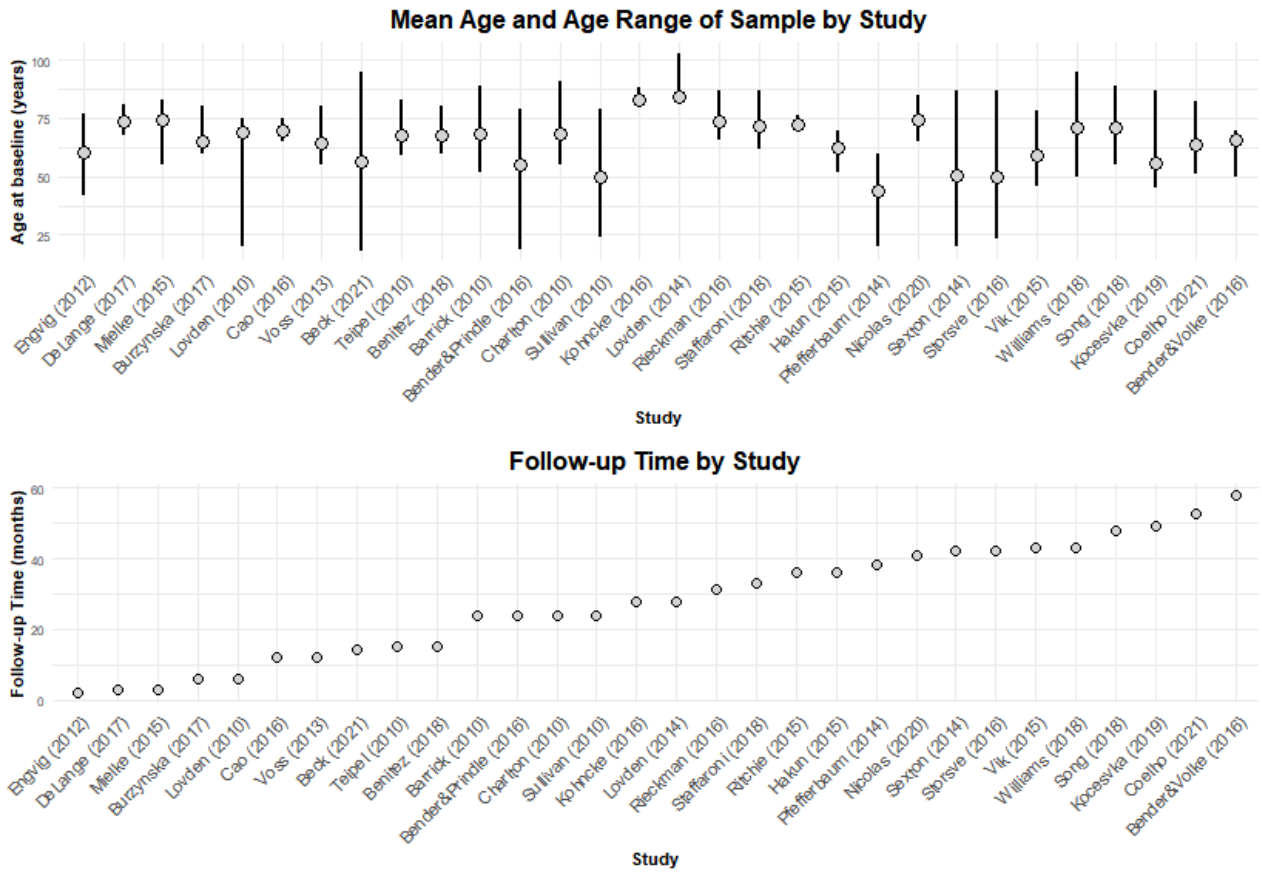


Figure 3.2

Combined plot of age range and mean age of sample, and follow-up time by study. Note. The top plot displays the mean age and age range for each study, ordered by follow-up time. The scatter plot below represents the mean follow-up time (in months) for each study.

Risk of bias (quality) assessment

AMC and an external reviewer assessed the risk of bias with the NIH quality assessment tool for observational cohort studies, case control studies, and pre-post studies with no control group (*Study Quality Assessment Tools | NHLBI, NIH*, 2013). Studies needed to have clearly defined aims, a clearly specified study population, appropriate inclusion criteria description, ethical approval, and healthy adults recruited from the community. In addition, AZB and AMC performed the quality check of the reported MRI methodology and statistics.

Data extraction

AZB and AMC independently extracted the following details using a structured data abstraction form: MRI method of WM microstructure quantification, study design (number and time between within-person measurements, longitudinal observational vs. intervention), anatomical specificity (global or regional measures of WM microstructure), participant demographics (sample size, age range, age at baseline, percentage of female participants), and results (statistically significant findings, measures of change, and their standard errors, Table 3.1).

Meta-analysis

Effect size estimation

Our meta-analyses focused on FA and two regions of interest: whole WM (n = 12) and genu of the corpus callosum (n = 9), as these regions allowed us to include the largest number of studies. We did not include MD, RD, AD, or other WM regions as few studies overlapped in reporting these DTI metrics and WM regions, resulting in a low number of studies available (see Table 3.1 for a summary of studies).

We used the R package 'metafor' to estimate the mean and standard deviation of the distribution of the outcome effect size using a random-effects model (Viechtbauer, 2010). For our effect size, we calculated Cohen's *d* or standardized mean difference (SMD) as the difference between two means (i.e., post-pre time measures), standardized by the pooled within-sample estimate of the population SD, calculated as SD (pooled within-sample) = $\sqrt{\frac{SD1^2 + SD2^2}{2}}$ where SD1 is the standard deviation for the baseline measurement and SD2 is the standard deviation for the follow-up measurement. We calculated the standard error of the SMD with the formula SE = $\sqrt{\left(\frac{1}{N}\right) + \left(\frac{SMD^2}{2N}\right) x \sqrt{2(1 - Corr)}}$ which accounts for the covariance between the two measurements and provides a more accurate estimate of the precision of the SMD, as recommended in the Cochrane Handbook (Section 23.2.7.2).

Heterogeneity analysis

We estimated heterogeneity using the I^2 statistic, which represents the percentage of variance between studies attributable to differences in true effect sizes across studies rather than sampling variability. Although there is no universal threshold for interpreting the I^2, values of 25%, 50%, and 75% are commonly used to denote low, moderate, and high heterogeneity, respectively. However, I^2 estimates may be imprecise because they are influenced by the precision of the individual study effect sizes and the presence of outliers (Ioannidis et al., 2007). To address this potential issue, we calculated 95% confidence intervals for the I^2 estimate using the Q-profile method (Viechtbauer, 2007).

Heterogeneity variance was calculated using the restricted maximum likelihood (REML) method (Langan et al., 2019). To further explore the heterogeneity of the effect sizes and the robustness of our meta-analysis, we employed Graphical Display of Study Heterogeneity

(GOSH) plots (Olkin et al., 2012) to display the effect sizes across studies. We then employed three supervised machine learning (k-means, DBSCAN, and the Gaussian Mixture Model) algorithms to detect clusters in the GOSH plot data and identify outlying and influential studies in our data. Lastly, to examine the potential for publication bias, we performed funnel plots and Egger's regression tests for funnel plot asymmetry.

Regions of interest for the meta-analyses

Whole WM FA was calculated as a mean of all regions-of-interest for the six studies (Barrick et al., 2010; Bender, Völkle, et al., 2016; Lövdén et al., 2014; Rieckmann et al., 2016; Storsve et al., 2016; Voss et al., 2013), whereas the other six-studies provided mean FA values for the whole WM using skeletonized data derived from Tract-Based Spatial Statistics (Beck et al., 2021; Burzynska et al., 2017; de Lange et al., 2017; Kocevska, Cremers, et al., 2019; Staffaroni et al., 2018; Teipel et al., 2010). Similarly, we included nine studies in the corpus callosum meta-analysis; we used data from the forceps minor for three studies (Lövdén et al., 2014; Storsve et al., 2016; Teipel et al., 2010).

Analysis of modifiers of change using individual-level data

Lastly, we performed linear mixed effects models using the lme4 package in R for a subset of studies (n = 6 studies, n = 375 subjects) that provided individual FA data (Beck et al., 2021; Bender, Völkle, et al., 2016; Burzynska et al., 2017; Rieckmann et al., 2016; Teipel et al., 2010; Voss et al., 2013). We added a random intercept for study and fixed effects for time point, age, sex, time until follow-up and sex-by-age interaction. To create partially standardized regression coefficients, we standardized all quantitative variables, but not factors. All analyses were conducted in R version 4.0.1, and statistical significance was accepted at $P < 0.05$ for two-tailed tests.

3.4. Results

Within-person changes in DTI parameters – a qualitative summary.

To provide a qualitative summary of within-person changes in DTI parameters, we analyzed 30 studies included in our systematic review. Of the 29 studies that reported changes in FA, 75% (22) reported significant negative changes in FA, six reported no change in FA (Engvig et al., 2012; Kocevska, Cremers, et al., 2019; Lövdén et al., 2010; Mielke et al., 2009; Sullivan et al., 2010; Voss et al., 2013) and only one reported both positive and negative changes in FA (Bender, Prindle, et al., 2016). It is noteworthy that the earlier studies tended to report no significant changes in FA (published 2009–2014). Of the 19 studies that reported changes in MD, 16 (84%) reported a significant increase in MD over time, whereas 3 reported no change (Lövdén et al., 2010; Sullivan et al., 2010; Teipel et al., 2010). Similarly, out of the 18 studies that reported changes in RD, 13 (72%) reported a significant increase in RD over time, 3 reported no change (Lövdén et al., 2010; Sullivan et al., 2010; Teipel et al., 2010) and 2 reported both positive and negative changes in RD (Bender, Prindle, et al., 2016; Cao et al., 2016). Among the 16 studies that reported changes in AD, 10 reported a significant increase in AD (62%), 5 reported no change (Cao et al., 2016; Lövdén et al., 2010; Sullivan et al., 2010; Teipel et al., 2010; Voss et al., 2013), and one reported both positive and negative changes in AD (Bender, Prindle, et al., 2016). See Table 3.1 for a summary of these studies.

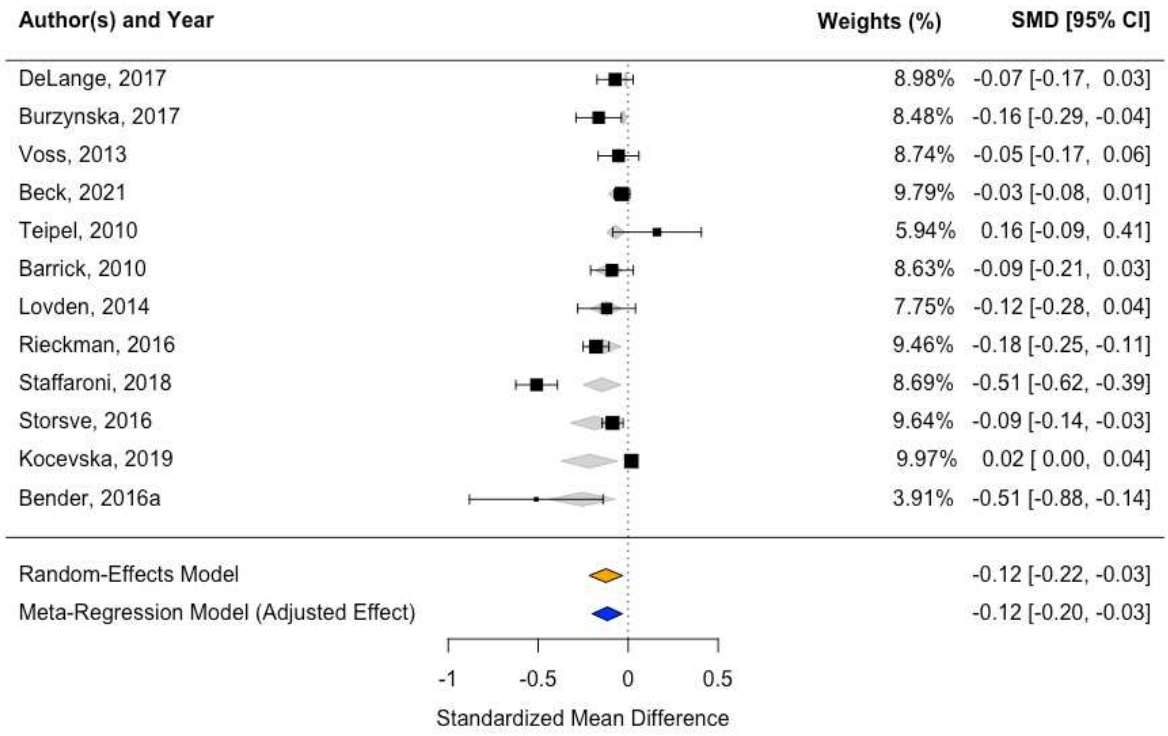
Within-person changes in FA of the whole WM – a meta-analysis

Due to the heterogeneity in reporting estimates of within-person change in DTI parameters, we performed a meta-analysis only on a subset of studies that provided sufficient data to calculate summary effect sizes and standard errors. For the whole WM, we obtained data from 12 studies (Fig. 3.3). The pooled effect showed a significant decline in the whole WM FA

(d = -0.1235, 95% CI: -0.21 to -0.03, p = 0.0086), both when adjusted or not adjusted for the follow-up time as a moderator. Heterogeneity across the studies was substantial (I^2 = 93.5% after adjusting for study follow-up time as a covariate).

Figure 3.3

Forest-plot showing standardized effects sizes of FA decline in the whole WM using summary statistics across 12 studies



Note. Box size represents study weights. At the bottom, we display final summary estimates with 95% CI for unadjusted vs. adjusted models (accounting for study follow-up time as a moderator). The weights for each study are calculated as the inverse of the variance of the effect size estimate for the study, meaning that the larger the standard error of an effect size estimate, the smaller the weight.

Table 3.1
Characteristics of the qualifying DTI longitudinal observational studies (n=30)

Authors	Year	Country/ Study	Follow-up	N, % female	Age (y)	DTI measure	WM regions	Statistics reported	Main results
Mielke et al.	2009	USA	3 m	25 HC, 56% 24 MCI, 28% 21 mild Alzheimer's, 28%	M=74 M=75 M=76	FA	FX, CING, SCC, CP	M±SE at t1 and t2	FA↓ in CING in MCI; No Δ in HC
Sullivan et al.	2010	USA	2 y	16 HC, 50%	24–40, 65–79	FA, RD, AD,	6 subsections of CC (tractography), midsagittal & distal sections	M±SD at t1 and t2 (as plots only)	No Δ
Barrick et al.	2010	UK/GENIE study	2 y	73 HC, 41%	50–90, M= 68.3	FA, RD, AD	Whole-skeleton voxelwise analysis; On WM skeleton:CC, IC, EX, CING, SCR	M±SD at t1 and t2, t2-t1	FA↓, RD↑, AD↑, Greatest Δ in GCC; No evidence for spatial gradient
Charlton et al.	2010	UK/GENIE study	2 y	73 HC, 43%	55-91, M=68.3	FA, MD	Whole WM	Normalized peak height freq., median±SD at t1 and t2	Histograms: ↓ FA and MD median & kurtosis
Teipel et al.	2010	Germany	13-16 m	11 HC, 36%, 14 MCI, 43%	60-88 59-83 M=67.4	FA	Regions on WM skeleton: CC, FX, CING, SLF	Annual %Δ	FA↓ in both groups (CC, CING, FX), no time-by-group interaction
	2010		6 m	HC: 10, 40%	20-30		5 subsegments of CC	M±SD at t1 and t2	No Δ in control group

			(RCT, cog. training)	HC: 13, 31%	65-76				
Lovden et al.		Sweden/COGITO		HC RCT: 20, 55%	22-30	FA, RD, AD, MD			
				HC RCT: 12, 58%	65-75				
Engvig et al.	2012	Norway	8 weeks (RCT, memory training)	HC: 20, 55%	42-77	FA, MD	Voxelwise on WM skeleton	% Voxels showing significant Δ, M±SD t2-t1 for significant voxels	MD↑, anterior-to-posterior gradient, No Δ in FA
				HC RCT: 21, 52%	M=60.3				
Voss et al.	2013	USA	1 y (RCT, walking)	HC Control: 35, 60%	60-80	FA, RD, AD	4 lobes on WM skeleton,	M±SD at t1 and t2, Annual %Δ	RD↑ in temporal lobe, No Δ in FA or AD
				HC RCT: 70, 64%	M=65		Voxelwise on skeleton (t2-t1)/t1		
Pfefferbaum et al.	2014	USA	1-8 y (M=3 y), 2-5t	56 HC, 57%, 46 alcoholics, 40%	20-60, M=44	FA, RD	Whole-skeleton analysis, post-hoc in clusters representing 27 regions	T, df and p value in clusters showing age differences (M at t1 and t2 only in plots)	FA↓ in both groups, RD↑
Lovden et al.	2014	Sweden/Swedish national Study on Aging and Care in Kungsholmen (SNAC-K)	2.3 y	HC 40, 55%	81-103, M=84	FA, MD	6 regions: CING gyrus, CST, Fmaj, Fmin, IFOF, SLF	M±SD at t1 and t2	FA↓, MD↑ in most regions

Sexton et al.	2014	Norway/ Cognition and Plasticity through the Lifespan	3-5 y (M=3.6 y)	HC 203, 59%	20-87, M=50.2	FA, MD, RD, AD	Whole-skeleton analysis, 4 lobes, significant clusters	Annual difference maps ((t2-t1)/y follow up), mean % Δ ((t2-t1)/(t1+t2/2)) ±SD	FA↓, MD↑, RD↑, AD↑. Greatest magnitude: frontal and parietal lobe. Superior-to-Inferior gradient
Hakun et al.	2015	USA	3 y	HC 18, 50%	52-70, M=62.4	FA	Voxelwise in whole WM, Tracts: BCC, GCC	No values reported for voxel-wise paired t-test. Individual %Δ in FA in BCC	FA↓ in GCC, BCC, clusters in association and projection tracts.
Ritchie et al.	2015	UK/Lothian Birth Cohort 1936	3 y	HC 488, 47%	72-76, M=73	FA	12 tracts: GCC, SCC, CING, CING gyri, ARC, UN, ILF, ATR	Factor loadings from latent change model (β and SE), controlled for age and sex	FA↓ in all tracts
Vik et al.	2015	Norway	M=3.6 y	HC 76, 68%	46-78, M=59	FA	Tractography: 19 frontal-subcortical, anterior callosal tracts, CST	M±SD of tracts at t1 and t2, annual %Δ, parametrized tract M and %Δ	FA↓ in anterior callosal fibers, No Δ in CST
Bender & Prindle et al.	2016	USA	2 y	HC 96, 69% 76 normotensives	19-79, M=55	FA, RD, AD	13 regions on WM skeleton: GCC, BCC, SCC, dorsal and ventral CING, UN, ALIC, PLIC, SLF, ILF, IFOF, FMaj, Fmin	Latent mean Δ (β /SE, d, ΔVar: latent variance in Δ parameter as β /SE) (for all and n=76 normotensive only)	

Bender & Völkle et al.	2016	USA	1-7 y 0-4 t	HC 35, 55%	50-70, M=65.4	FA, RD, AD	12 regions on WM skeleton: CING, IFOF, ILF, SLF, UN, ALIC, PLIC, GCC, BCC, SCC, FMaj, Fmin	LME model: β, SD, SE for regions grouped as association, commissural, projection	AD↓, FA, RD↓ in association and projection fibers, AD, FA↓, RD↑ in GCC and Fmin; Anterior-to-posterior gradient
Storsve et al.	2016	Norway/ Cognition and Plasticity through the Lifespan	3-5 y (M=3.6 y)	HC 201,59%	23-87, M=50	FA, MD, RD, AD	18 major tracts: Fmin, Fmaj, ATR, Angular and cingular CING, CST, ILF, SLF, UN	Annual %Δ±SD	AD↓ and FA↓ in association regions, RD↓ in association and commissural regions. Last-in first-out gradient
Rieckman et al.	2016	USA/ Harvard Aging Brain Study	M=2.6 y	HC 108, 56%	66-87, M=73.7	FA, MD, RD, AD	12 regions: SLF, superior frontal occipital, IFOF, ACR, SCR, PCR, IC, GCC, BCC, SCC, CING, parahippocampal CING	Intercept at 66 and M annual Δ% (without variability in Δ)	RD> MD> AD>FA↓, Right>Left, Superior-to-Inferior gradient
Kohncke et al.	2016	Sweden/Swedish National Study of Aging	2.3 y	HC 37, 58%	88-88, M=83.2	FA, MD	CST	M±SD, skewness, kurtosis for t1 and t2, t2- t1±SD, unstandardized effects for Δ after controlling for age, edu and sex.	Overall FA↓ MD↑, less regions affected by RD↑ and AD↑
Cao et al.	2016	China	1 y	HC Control: 14, 38%	M=70	FA, MD, RD, AD	WM skeleton: t2-t1	Maps of whole-WM comparisons, cluster size and peak p value	FA↓ MD↑

			(12-week cog. training)	HC RCT: 34, 36%	M=69				
Burzynska et al.	2017	USA/Fit and Active Seniors	6 m (RCT, walking, dance, nutrition)	Total: 174, 69% HC Control: 40, 68%	60-80 M=65	FA, MD, RD, AD	CING, ALIC, Fmaj, Fmin, FX, gyrus rectus, HIPP, ILF, IFOF, PCC, PLIC, 6 subsections of CC, UN, PFC, whole WM	%Δ M±SD	HC: FA↓, RD↑, MD↑, AD↑
De Lange et al.	2017	Norway/ Neurocognitive Plasticity	10 weeks (RCT, memory training)	HC: 49 HC: 28	M=73.4 M=26.1	FA, MD, RD, AD	Voxelwise on WM skeleton	MD (plots only), only group x time interaction, no statistics for longitudinal ΔDTI reported	FA↓, RD↑, MD↑, AD↑
Song et al.	2018	USA/Dallas Lifespan Brain Study (DLBS)	4 y	HC 52, 73%	55-89, M=70.7	FA, RD, AD	parahippocampal CING, FX, whole WM	t1 and t2 RD in FX (on plots), annual change rate (R^2, p), β and SE for annual Δ rate	Not reported (mentioned FA↓, RD↑, MD↑, AD↑ in control but unclear if it was significant)
Benitez et al.	2018	USA	M=15.2 m	HC 39, 72%	60-80, M=67.7	FA, MD	Regions on WM skeleton: GCC, BCC, SCC, CP, CST, CING, FX, PLIC, SLF, SS, SFOF; UN	Annual %Δ M±SD	FA↓, MD↑
Staffaroni et al.	2018	USA	2.9 y	HC 69, 58%	61-87, M=71.7	FA, MD	FX	Annual Δ (β±95 CI)	FA↓, MD↑ in FX
	2018	USA/Baltimore	3.6 y	HC 406, 58%		FA, MD	Regions: SLF, SFO, IFOF, SS, CING gyrus		FA↓ MD↑

Williams et al.		Longitudinal Study of Aging			50-95, M=71.3		and hippocampus, GCC, BCC, SCC, ACR, SCR, PCR, ALIC, PLIC	Annual Δ (β±95 CI and t-values from LME)	
Kocevska et al.	2019	Netherlands/Rotterdam Study	5.2 y (2.8-8.1y)	HC 2125, 56	45-87, M=56	FA, MD	Global WM and tracts: Brainstem, CST, ATR, STR, PTR, SLF, ILF, IFOF, UN, CING gyrus, CING parahippocampus, FX, Fmin, Fmaj	Global WM FA and M±SD at t1 and t2	No change in FA
Nicolas et al.	2020	France/Agrica MSA IFR de Santé Publique	3.4 y	HC 130, 47 APOE e4+, 27	65-85, M=74.1	MD	Whole WM on WM skeleton	t2-t1 (M±SD)	↑MD in frontal WM (mostly anterior CC), CING, SLF, FX
Beck et al.	2021	Norway/Tematisk Område Psykoser and StrokeMRI	1.2 y	HC 258, 33%	18-95, M=55.6	FA, MD, RD, AD	Voxelwise for whole WM	Fixed effect of time (β±SD) predicted Δ with age plotted as derivative values.	FA↓, RD↑, MD↑, AD↑
Coelho et al.	2021	Portugal/Switchbox consortium	4.3 y	HC 51, 51%	51-82, M= 63.5	FA, MD, RD, AD	Regions were organized in clusters of ROIs that varied by DTI metric.	Annual %Δ and slopes by clusters of ROIs not by individual ROI.	FA↓ in CC, SCR, PCR, ALIC, EC and SLF. MD↑, AD↑ in CC, CP, IC, CR, thalamic radiations, EC, FX, SLF, SFOF

*Note***.** Only information relevant for DTI is included (other diffusion metrics or volumetric data are not reported). AD: axial diffusivity, ALIC: anterior limb of internal capsule, ARC: arcuate fasciculus, BCC: body corpus callosum, BP: blood pressure, BMI: body mass index, CC: corpus callosum, CING: cingulum, CP: cerebral peduncles, CST: corticospinal tract, Δ: change, EC: external capsule, FA: fractional anisotropy, Fmaj: forceps major, Fmin: forceps minor, FX: fornix, GCC: genu corpus callosum, HC: healthy controls, IFOF: inferior frontal-occipital fasciculus, IC: internal capsule, ILF: inferior longitudinal fasciculi, LME: linear mixed effect, M: month, MD: mean diffusivity, PCC: posterior cingulate cortex, RD: radial diffusivity, SCR: superior corona radiata, SLF: superior longitudinal fasciculus, SFOF: superior frontal-occipital fasciculus, t1: time point 1, t2: time point 2, WMH: white matter hyperintensities, y: year.

To address the high heterogeneity, we performed diagnostic testing for influential cases (outliers) with GOSH plots, followed by sensitivity analyses, which identified two outlier studies (Kocevska, Cremers, et al., 2019; Staffaroni et al., 2018). We repeated the random effects model without the two outliers, which confirmed the significant negative change in FA shown in Figure 3.3 (see Table 3.2 for model comparisons), but with reduced heterogeneity (residual $I^2 = 48\%$) (Fig. 3.4). The reduction in heterogeneity indicates that approximately 48% of the total variance in FA can be attributed to heterogeneity among the studies, with the remaining 2% attributed to sampling variance. In sum, the model comparison indicated a robust and significant effect size of within-person decline in FA in the whole WM despite the heterogeneity observed among the studies.

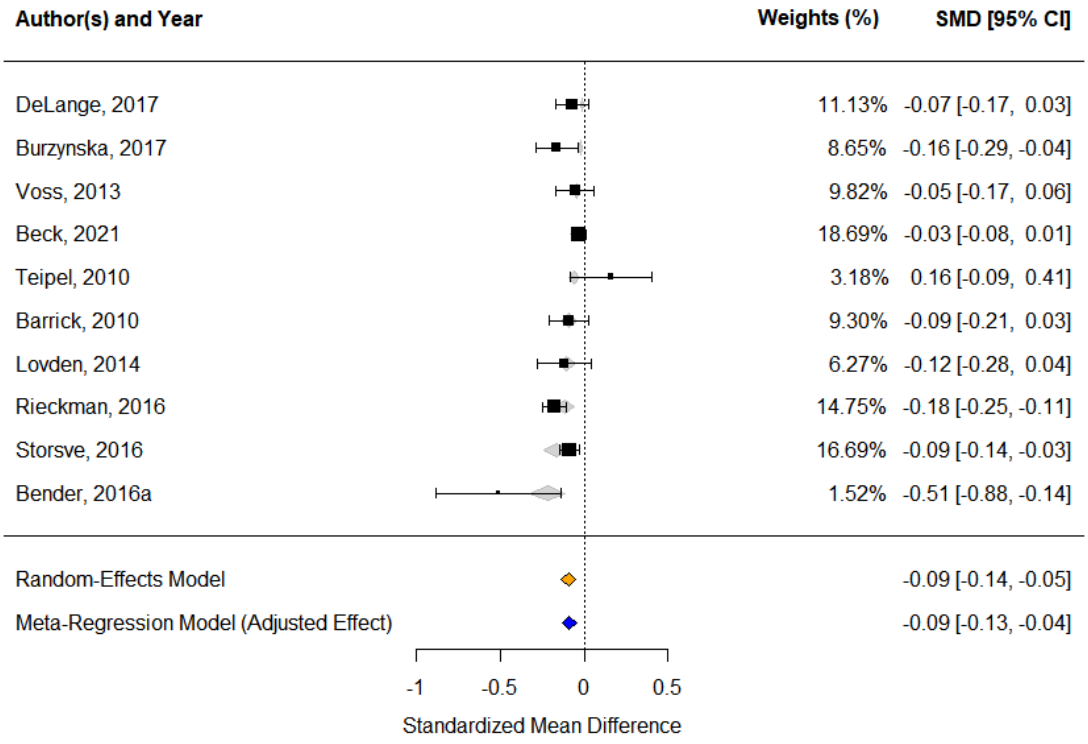


Figure 3.4

Forest-plot showing standardized effects of total FA change across all studies after omitting outliers (Staffaroni, 2018 and Kocevska, 2019). Note. Box size represents study weights. At the bottom, we display final summary estimates with 95% CI for the random-effect model.

Table 3.2. *Meta-analysis: comparison of the full model and with excluded influential studies*

Analysis	*N*	*Age*	*d*	95% CI	*p*	I^2	95% CI of the I^2
Main Analysis (Fig. 3.3)	2906	66.4	-0.12	-0.21; -0.03	0.008	95 %	88.7; 98.6
Influencing Cases Removed (Fig 3.4) *	724	66.6	-0.09	-0.13; -0.04	<0.001	49 %	12.54; 96.89

Note. *Removed as outliers: Staffaroni et al., 2018 and Kocevska et al., 2019.

Within-person changes in FA of the genu corpus callosum – a meta-analysis

For the genu corpus callosum, we obtained data from 9 studies. The pooled effect among 550 participants (69.2 ± 6.8 years old) showed a significant negative change of the FA in the genu (d = -0.1432, 95% CI: -0.22 to -0.06, p = 0.0003, Fig. 3.5), with a moderate level of heterogeneity (residual I^2 = 65%).

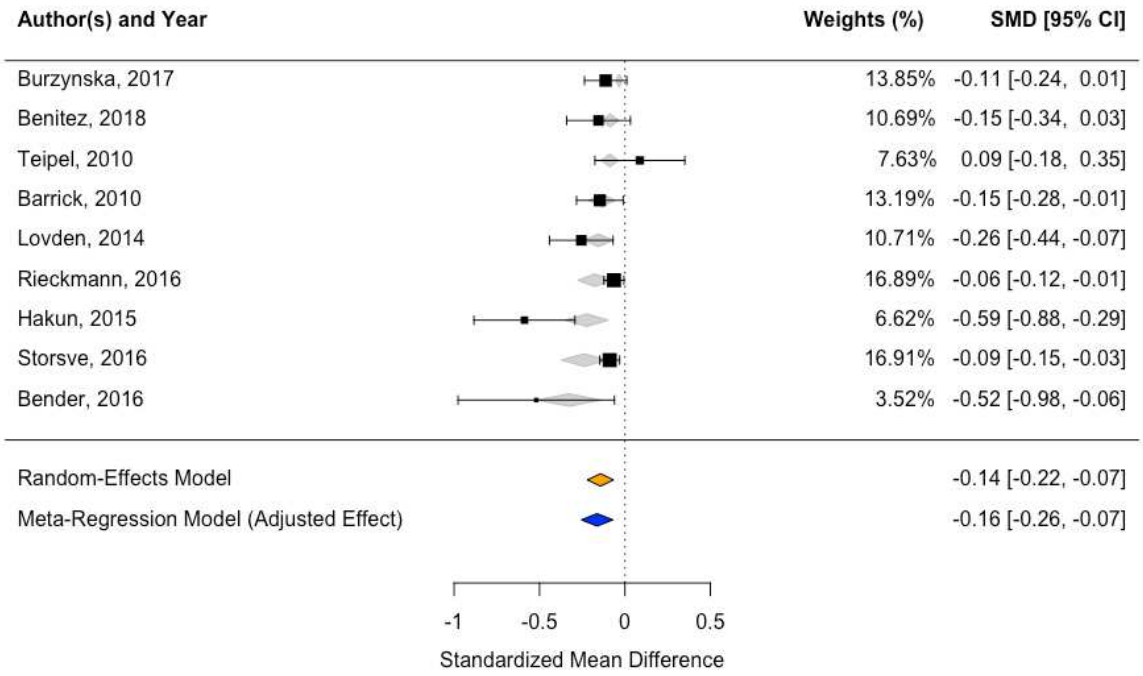


Figure 3.5
Forest-Plot Showing Standardized Effects of FA Change in the Genu of the Corpus Callosum Across Nine Studies Note. Box size represents study weights. At the bottom, we display final

summary estimates with 95% CI for unadjusted vs. adjusted models accounting for study follow-up time as a moderator.

The effect of follow-up time on change in FA

To understand the effect of follow-up time (i.e,. the time elapsed between the two measurements) on FA change, we correlated the mean % change in both whole WM and genu FA with the mean study follow-up time. We found a trend towards increased decline in FA with longer follow-up times in both the whole WM (r = -0.28, 95% CI: -0.74 to 0.34, p = 0.361) and the genu of the corpus callosum (R = -0.53, 95% CI: -0.88 to 0.19, p = 0.134) (Fig. 3.6).

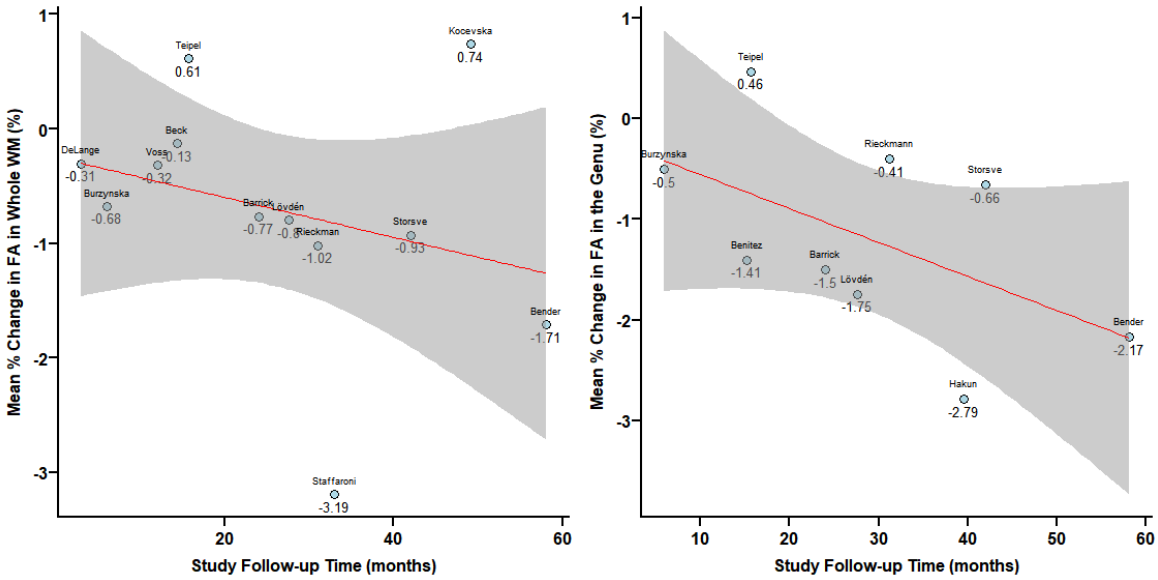


Figure 3.6

Correlation Between the Mean % Change in FA and Mean Study Follow-Up Time. Note. The regression lines represent the results of a linear model fitted to the data. The shaded area around the line represents the standard error. Points display the percent change for each study.

The effect of age and sex on change in FA

To examine the effects of age and sex on within-person changes in DTI parameters, we took a two-step approach. First, we conducted a qualitative analysis of the studies that included

age and sex as co-variates in their analyses. Next, we performed quantitative analysis on the studies that provided individual FA data at both timepoints (see below).

Out of the twelve studies that reported effects of age, older age was associated with a greater magnitude of the decline in FA in eight studies (Beck et al., 2021; Bender, Prindle, et al., 2016; Bender, Völkle, et al., 2016; Burzynska et al., 2017; Pfefferbaum et al., 2014; Sexton et al., 2014; Storsve et al., 2016; Williams et al., 2019), one study reported no effect of age (Barrick et al., 2010) and one study did not investigate the effect of age on the magnitude of change in FA (Song et al., 2018).

Older age was also associated with greater increase in MD in seven studies (Beck et al., 2021; Charlton et al., 2010; Engvig et al., 2012; Lövdén et al., 2014; Nicolas et al., 2020; Storsve et al., 2016; Williams et al., 2019), increase in RD in four studies (Beck et al., 2021; Bender, Völkle, et al., 2016; Sexton et al., 2014; Storsve et al., 2016) and increase in AD in five studies (Beck et al., 2021; Bender, Prindle, et al., 2016; Bender, Völkle, et al., 2016; Sexton et al., 2014; Storsve et al., 2016). Of note, three studies across the lifespan specifically reported an accelerated decline in FA after the fifth decade of life (Beck et al., 2021; Sexton et al., 2014; Storsve et al., 2016). Specifically, Beck et al (2021) reported that FA decreased steadily after age 30, with a steeper decline after age 50. Meanwhile, MD, AD, and RD decreased until the 40s but subsequently increased.

Sex differences in within-person changes in DTI parameters were reported in seven studies. Two studies (28%) reported significant sex differences in DTI changes (Lövdén et al., 2014; Williams et al., 2019). Specifically, Williams et al (2019) found that women showed greater decline in FA in the cingulum and greater MD increase in the genu of the corpus callosum. In contrast, in a study of very old adults, Lövdén et al (2014) found that women had a

smaller decline in FA in the forceps minor than men. However, most studies found no significant sex differences in DTI changes (Beck et al., 2021; Burzynska et al., 2017; Nicolas et al., 2020; Sexton et al., 2014; Teipel et al., 2010).

Next, we performed a regression analysis using aggregated data from studies that supplied individual-level FA data (Beck et al., 2021; Bender, Völkle, et al., 2016; Burzynska et al., 2017; Rieckmann et al., 2016; Teipel et al., 2010; Voss et al., 2013). A linear mixed-effects model showed that older age, female sex, longer follow-up time, and the interaction of age and sex were associated with greater declines in FA in the whole WM. The age-sex interaction revealed that the negative effect of age on FA change was more pronounced in females than in males. Table 3.3 and Figure 3.7 present the results of this analysis. We did not perform this analysis for the genu of the corpus callosum, since only 3 studies provided individual FA data.

Table 3.3

Linear mixed-effects analysis of within-person change in the whole WM

	Unadjusted estimates			Full model		
Model parameter	***β***	**SE**	***p***	***β***	**SE**	***p***
Intercept	0.567	0.552	0.305	0.589	0.540	0.203
Age (baseline)	-0.298	0.024	0.001	-0.237	0.032	0.001
Time until follow-up	-0.061	0.044	0.166	-0.066	0.116	0.001
Sex	-0.206	0.045	0.001	-0.196	0.041	0.001
Sex-by-age interaction	-0.124	0.040	0.002	-0.124	0.040	0.002

Number of observations: 750. Number of groups (random effect by studies): 6. Sex is coded as 0 for males and 1 for females. *β* are standardized. The model estimates the effects of various predictor variables on the change in whole WM FA over time, including age at baseline, time until follow-up, sex, and a sex-by-age interaction.

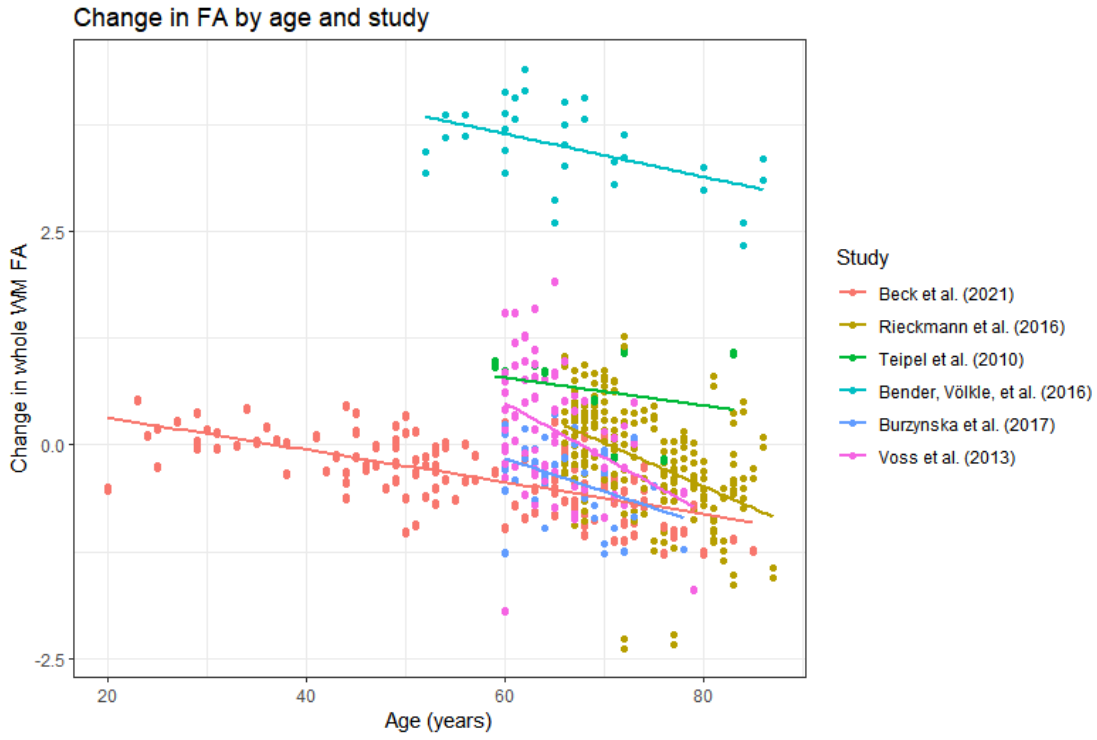


Figure 3.7
Within-person change in the whole WM by study with individual FA data. Note. The plot shows the change in the whole WM FA by age and study. Each point represents an individual's predicted FA change. The solid lines represent the linear regression line for each study.

Spatial patterns of within-person changes: qualitative summary

Due to the wide variability in defining regions of interest among the 30 studies in Table 3.1, we could not directly compare the effect sizes of FA change across different regions in a meta-analysis. Thus, we offer a qualitative summary of our findings.

In brief, only three studies have supported the development-to-degeneration pattern of WM decline (Bender, Prindle, et al., 2016; Bender, Völkle, et al., 2016; Storsve et al., 2016). However, our systematic review indicated that, generally, older age was associated with greater longitudinal changes in FA, MD, and RD in late-myelinating regions, such as the genu of the corpus callosum, anterior limb of the internal capsule, and fornix, compared to early myelinating

regions, such as the superior corona radiata, posterior limb of the internal capsule, and corticospinal tract (Barrick et al., 2010; Bender, Völkle, et al., 2016; Teipel et al., 2010; Vik et al., 2015). Similarly, two studies (Burzynska et al., 2017; Song et al., 2018) reported the greatest magnitude of decline in FA in the fornix, a late-myelinating tract that reaches peak myelination more than 144 weeks after birth (Kinney & Volpe, 2018). However, none of these studies directly compared the rate of change between the late-and early myelinating regions.

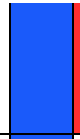
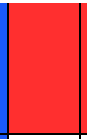
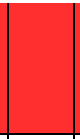
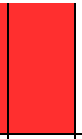
Interestingly, eight studies reported the largest within-person change observed in the genu of the corpus callosum (Barrick et al., 2010; Benitez et al., 2018; Hakun et al., 2015; Lövdén et al., 2014; Nicolas et al., 2020; Pfefferbaum et al., 2014; Teipel et al., 2010; Vik et al., 2015), which aligns with both the anterior-to-posterior gradient and development-to-degeneration pattern of WM deterioration. This anterior-to-posterior gradient was more evident in studies with younger participants, with mean ages ranging from 59 to 68 years (Barrick et al., 2010; Benitez et al., 2018; Teipel et al., 2010; Vik et al., 2015). Conversely, studies examining older adults aged 70 years or older, reported a change in FA, MD, and RD in early myelinating regions, such as the corticospinal tract and projection fibers, such as the superior and posterior corona radiata (Köhncke et al., 2016; Lövdén et al., 2014; Rieckmann et al., 2016). One of the earliest studies to report the differential effects of age among different WM regions was conducted by Lövdén et al. (2014), who found that the rate of change in MD over time was less pronounced in the oldest old, particularly in early myelinating tracts. Importantly, none of the studies have investigated the time-by-region interaction, which would provide insight into the temporal changes in WM deterioration across different WM regions.

In contrast, a few studies demonstrated more widespread WM over time, with no clear evidence of spatial gradients of WM change (Cao et al., 2016; Coelho et al., 2021; Williams et

al., 2019). While other studies only reported changes in one region of interest, we were unable to compare changes in WM among different regions (Beck et al., 2021; Charlton et al., 2010; de Lange et al., 2017; Köhncke et al., 2016; Staffaroni et al., 2018). Table 3.4 summarizes the aforementioned regional differences in WM changes.

Table 3.4. Within-person change in DTI metrics, moderators of change and regional differences.

Study	FA	MD	RD	AD	WM regions with the largest within-person change	Moderators of WM change
Mielke et al., 2009		-	-	-	-	-
Sullivan et al., 2010					-	-
Barrick et al., 2010		-			Greatest RD↑, AD↑ in the GCC, followed by SCC and ALIC. Greatest FA↓ in the GCC, followed by SCC and superior posterior cingulum	Baseline age, BMI, BP, smoking, cholesterol levels and WMH volume: not related to Δ in RD, AD, FA
Charlton et al., 2010			-	-	*	Age↑: greater ↑ΔMD but not FA
Teipel et al., 2010					Greatest ↓ in FA was observed in CING, followed by FX, GCC	No effects of sex or APOE genotype on rate of ΔFA
Lovden et al., 2010					-	ΔMD↑ in both young and old (↑FA only in old) in genu after 100 h cog. Training
Engvig et al., 2012			-	-	-	Age↑: greater ↑ΔMD. Memory training: ↓ΔFA in anterior WM
Voss et al., 2013		-			-	No effect of intervention on DTIΔ
Pfefferbaum et al., 2014		-		-	Greatest ↓ in FA was observed in GCC, followed by BCC and ACR, with the smallest effect in the EC.	Alcohol use status: FA↓ and RD↑ in heavy drinking relapsers >light drinking relapsers > total abstainers. Age↑: greater FA↓ in both groups
Lovden et al., 2014			-	-	Greatest ↑ in MD observed in GCC and Fmin.	Age↑: lesser MD↑ in IFOF and SLF. Years of education: greater FA↓ in Fmin, Women: lesser FA↓ in Fmin; FA↓, MD↑ in CST correlated with decline in processing speed
Sexton et al., 2014					Frontal and parietal lobe with >49% of significant voxels.	Age↑: greater FA↓, ↑MD, RD, AD, acceleration of Δ after the 5th decade, mostly in frontal and parietal lobes;

						attenuated if controlled for WMH. No sex differences but a greater acceleration of FA↓ with age in men.
Hakun et al., 2015		-	-	-	Greatest ↓ in FA observed in GCC, followed by BCC.	FA↓ correlated with BOLD response ↑ in the prefrontal cortex
Ritchie et al., 2015		-	-	-	Not reported	↑FA at baseline associated with less steep decline in fluid intelligence
Vik et al., 2015		-	-	-	Greatest magnitude of decline in GCC, minimal change in CST	-
Bender, Prindle, et al., 2016		-			AD↑ and FA↓ in ALIC and Fmin.	Age↑: AD↑ in ALIC, FA↑ in BCC, FA↓ ALIC and Fmin. Metabolic syndrome score (log-transformed triglyceride level, systolic blood pressure, waist-to-hip ratio, and fasting blood glucose level) was not associated with DTIΔ
Bender, Volke, et al., 2016		-			Association fibers showed the greatest decline. Projection fibers showed the smallest magnitude of Δ.	Age↑: AD↑ in association fibers, RD↑ in commissural fibers, FA↓ in association fibers. Hypertension diagnosis weakly associated with RD↑
Storsve et al., 2016					Greatest magnitude of Δ was apparent for RD, MD and AD in the CING-cingulate gyrus and SLF. Greatest magnitude of Δ for FA was in the ATR, followed by the CING and SLF.	Age↑: greater FA↓, ↑MD, RD, AD. Cortical thinning, greater ↑MD and ↓FA
Rieckman et al., 2016					Greatest magnitude of Δ in FA, RD, MD in the parahippocampal CING, followed by the SFOF and IFOF.	Amyloid burden: FA↓ and RD↑ in the parahippocampal CING
Kohncke et al., 2016				-	*	WMH volume: FA↓ and MD↑
Cao et al., 2016					RD↑ in the left posterior radiata, left CING of the cingulate gyrus, and left SLF. FA, MD more widespread Δ.	Cog. Training: reduced AD↑

Burzynska et al., 2017					Greatest magnitude of Δ for FA was in the FX, followed by the PLIC, EC, ACC and ALIC.	Age↑: greater FA↓ in Fmaj; Baseline MVPA: lesser FA↓ in PFC; sedentary time: greater FA↓ in CC and prefrontal WM; no effect of baseline cardiorespiratory fitness or sex
De Lange et al., 2017					*	Older training group: reduced FA↓, RD↑, MD↑, AD↑, than the younger training group
Song et al., 2018		-			Greatest magnitude of Δ was found in RD of the FX.	↑Neocortical Aβ Burden (PET): RD↑ in FX, controlling for age and sex
Benitez et al., 2018			-	-	FA and MD greatest magnitude in GCC and projection fibers.	-
Staffaroni et al., 2018			-	-	*	Telomere attrition↑: greater FA↓ and MD↑ in FX, controlling for physical activity and vascular risk
Williams, 2018			-	-	FA showed significant rates of decline over time across the whole brain except the SLF, GCC and PLIC. MD showed significant rates of increase over time across the whole brain except the GCC	Age↑: greater FA↓ in FX and MD↑ in association fibers.
						Vascular burden: greater FA↓ in CING. APOE e4: greater FA↓ in GCC and SCC. Women: greater FA↓ in CING, greater MD↑ in GCC. Adjusted by sex, race, and scanner type.
Kocevska et al., 2019		-	-	-	-	Sleep duration or quality not related to DTIΔ.
Nicolas et a., 2020	-		-	-	Frontal WM regions, mostly GCC	Age↑: greater MD↑, independent of sex, education and APOE e4
Beck et al., 2021					*	Age↑: FA↓ accelerated after the 5th decade. MD, AD, RD showed steady ↑, accelerated after age 60. Sex: no effect.
Coelho, et al., 2021					Widespread WM change	↑Δ L>R hemisphere. Greater Δ in all DTI metrics led to reduced executive function and memory

Note. The color-coding in the heat map is used to represent the direction of change in DTI-MRI parameters (FA, MD, RD, AD). A positive change is represented by red and a negative change is represented by blue. The color grey is used to represent no change. The color orange represents positive and negative changes. ACR: anterior corona radiata, AD: axial diffusivity, ALIC: anterior limb of internal capsule, ATR: anterior thalamic radiation, BCC: body corpus callosum, CC: corpus callosum, CING: cingulum, CST: corticospinal tract, Fmaj: forceps major, Fmin: forceps minor, FA: fractional anisotropy, FX: fornix, GCC: genu corpus callosum, ILF: inferior longitudinal fasciculi, MD: mean diffusivity, MVPA: moderate-to-vigorous physical activity, PLIC: posterior limb of internal capsule, RD: radial diffusivity, SCR: superior corona radiata, SLF: superior longitudinal fasciculus, WMH: white matter hyperintensities. Δ: change, * studies with only one region or tract of interest.

Other modifiers of within-person changes in DTI: lifestyle, genetics, and cognitive status

Physical activity and social activities

Engagement in leisure activities with a strong social component (e.g., going to a concert or to the theater) over a 3-year period was associated with positive changes in WM in the corticospinal tract and greater processing speed in individuals older than 80 years (Köhncke et al., 2016). In addition, previous randomized controlled trials have shown subtle effects of aerobic exercise on changes in WM measured with DTI (Burzynska et al., 2017; Voss et al., 2013). Results from Voss (2013) showed that while aerobic fitness training did not affect group-level changes in WM integrity, executive function, or short-term memory, greater aerobic fitness derived from a walking program (walking 3-times per week) was associated with greater increase in WM integrity in the frontal and temporal lobes and greater improvement in short-term memory. Finally, a recent study by Burzynska (2017) found that a 6-month, 3-times per-week dance intervention resulted in a significant time-by-group interaction in the fornix, where the dance group showed a lower rate of decline in FA and an increase in RD than the control and walking groups.

Cognitive Training

Memory training has also been shown to induce experience-dependent plasticity, which was associated with a reduced decline in FA in the anterior WM as compared to controls (Engvig et al., 2012). Similarly, a 100-hour cognitive training program found positive changes in FA in the genu of the corpus callosum in the older training group but not in the younger training group (Lövdén et al., 2010). This was later replicated by De Lange et al (2017), who found a pattern of higher FA values, and lower MD, AD, and RD values in the older cognitive training group. So far, only Cao et al (2016) found decreased AD without significant changes in FA, MD, or RD

after a 12-week cognitive training intervention. However, another 12-week cognitive training intervention failed to find significant effects on change in DTI paremeters (Lampit et al., 2015).

Hypertension and alcohol consumption

Heavy-drinking relapsers had steeper decline in FA compared to abstainers, in areas such as the anterior commissural tracts (genu and body), projection fibers (corona radiata, external capsule, internal capsule anterior limb), and association fibers (superior longitudinal fasciculus)(Pfefferbaum et al., 2014). In addition, cardiovascular risk factors have been identified as potential moderators of within-person changes in WM: Williams et al., (2019) reported that higher baseline vascular burden (i.e., hypertension, obesity, elevated cholesterol, diabetes and smoking status) was associated with greater decline in FA in the parahippocampal cingulum, fornix/stria terminalis and splenium of the corpus callosum and greater increases in MD in the splenium of the corpus callosum in healthy older adults. However, another study suggested only trend-level associations between diagnosed hypertension and within-person increases in AD and RD (Bender, Völkle, et al., 2016).

Genetic risk factors and cognitive status

APOE ε4 carriers had a significantly greater decline in FA in the genu and body of the corpus callosum and splenium of the corpus callosum compared to non-carriers, but did not differ in rates of change in MD (Williams et al., 2019). Moreover, in healthy older adults, higher amyloid burden has been linked to faster FA decline in the parahippocampal cingulum, body corpus callosum, and forceps minor (Rieckmann et al., 2016). In addition, Racine et al. (2019) found that the levels of phosphorylated tau protein (p-tau) and beta-amyloid 42 (Aβ42), both of which are biomarkers of Alzheimer's Disease, were associated with baseline FA and MD, while the biomarker YKL-40 predicted greater within-person changes in MD over time. Furthermore,

Song et al. (2018) found that amyloid-beta burden was associated with a greater decline in RD in the fornix, even after adjusting for age and sex. Interestingly, another study reported an interaction between APOE ε4 status and lifestyle: light physical activity was associated with greater increases in MD and AD among healthy adults with APOE ε4 genotype, when compared to noncarriers (Raffin et al., 2021). In line with this, low physical activity levels were associated with decrease in MD in subjects with subjective cognitive impairment (Maltais et al., 2020). Finally, Fletcher et al. (2013) found that greater within-person changes in AD in the fornix were associated with an increased risk of conversion to mild cognitive impairment in healthy older adults (Fletcher et al., 2013). In contrast, Teipel et al. (2010), did not find greater within-person change in FA in participants with mild cognitive impairment compared to the healthy controls; however, they observed that the trajectories of change were more variable in participants with mild cognitive impairment than in healthy aging.

3.3. Discussion

Our study supported our overarching hypothesis that WM microstructure undergoes significant within-person changes in older age and that these changes can be captured using DTI. We found that within-person changes in WM microstructure in older age predominantly involve declines in FA and increases in MD and RD. Furthermore, our results showed that the magnitude of within-person change increases with advancing age. We also found that within-person changes in WM microstructure follow the development-to-degeneration spatiotemporal pattern, with greater magnitude of change in late-myelinating regions. Moreover, our results provided mixed evidence for the effect of sex, hypertension, lifestyle factors, and genetic polymorphisms in moderating the within-person changes in WM microstructure. Due to the high heterogeneity

between the studies included in this review, we offer recommendations for future longitudinal studies examining within-person change in WM in older adults at the end of the discussion.

What is the magnitude and direction of within-person changes in adult WM microstructure?

We found consistent changes in DTI parameters over time, particularly increases in MD, RD, and AD, and decreases in FA. Our qualitative analyses found predominantly declines in FA and increases in MD and RD. As expected, we observed a negative change in the whole WM and genu of the corpus callosum over time. While we found substantial heterogeneity among the studies, the significant effect size found in this meta-analysis indicated that the decline in FA was a robust finding despite the variability observed among the studies.

Magnitude of the effect

The findings of our study indicate a significant decline in FA in older adults at a rate of approximately -0.7% in most studies. This aligns with previous longitudinal studies examining WM changes in aging individuals, which have reported similar decline rates (Barrick et al., 2010; Sexton et al., 2014; Teipel et al., 2010). Specifically, we observed a percentage change in WM ranging from 0.7% to -3% for the whole WM. However, it is important to note that we could not calculate an effect size estimate per year due to varying follow-up times across studies (ranging from 2 to 58 months), as only two studies had a 12-month follow-up duration (Cao et al., 2016; Voss et al., 2013). We did not standardize our effect size estimates per year since assuming a linear trajectory of change across all studies could lead to biased effect size estimates. Therefore, it is important to acknowledge the limitations of our current understanding of the rate of decline in FA in WM in aging individuals, given the variability in follow-up durations and potential non-linear trajectories of change. Future studies with more uniform follow-up durations would be needed to estimate the effect size of this decline more accurately.

Do within-person changes in white matter microstructure accelerate with age and is there a tipping point?

Our qualitative review suggests that within-person changes in WM microstructure do accelerate with age, particularly after the fifth decade of life. Specifically, three studies reported an accelerated decline in FA after age 50 (Beck et al., 2021; Sexton et al., 2014; Storsve et al., 2016). Moreover, older age was consistently associated with greater decline in FA and greater increase in MD, RD, and AD in most studies.

The linear mixed effects model also showed that older age was associated with greater declines in FA in the whole WM, and that this negative effect of age on FA change was more pronounced in females than males. The estimate for the effect of age on FA change was β=-0.298, indicating that for each additional year of age at baseline, there was an average decrease of 0.298 in FA. The effect of age on FA change remained significant after adjusting for sex and follow-up time. However, further research is needed to determine if there is a specific tipping point at which these changes become more pronounced. Additionally, given the greater within-person decline in older women, further investigation of sex differences in within-person changes in WM microstructure is warranted.

What are the time periods over which WM microstructural decline can be detected in healthy adults using Magnetic Resonance Imaging?

We did not find a significant effect of follow-up time as a moderator of within-person change in the meta-analysis. The lack of a significant effect of follow-up time on our meta-analysis may have been due to insufficient power to detect small differences. When we analyzed individual-level data for FA from a subset of 375 participants using linear mixed effects modeling, we observed a significant effect of time until follow-up on within-person change. This

suggests that our meta-analysis may have lacked the power to detect the effect of follow-up time on within-person change.

Our qualitative review found that earlier studies with follow-up times of less than six months and small sample sizes did not find significant within-person changes in WM (Lövdén et al., 2010; Mielke et al., 2009). In contrast, more recent studies have started to report small but significant effects at shorter follow-up times. For example, Engvig (2012) reported significant within-person change in MD after only two months but not in FA. Similarly, DeLange (2017) showed a decline in FA and increases in MD, RD, and AD in healthy controls compared to the memory training group after a 3-month follow-up.

We observed significant within-person change in all DTI metrics at 6-months follow-up time (Burzynska et al., 2017). Studies with follow-up times ranging from 6- to 58 months consistently reported a decline in FA and increases in MD, RD, AD over time. However, we found some exceptions with no significant results (Kocevska, Cremers, et al., 2019) or mixed findings (Bender, Prindle, et al., 2016; Cao et al., 2016).

Our findings suggest that changes in WM can be detected within a short period of 3 to 6 months. However, results are more consistent when the follow-up time is longer. This indicates that follow-up times shorter than six months may not be sufficient to detect within-person changes in WM microstructure in healthy adults, mainly when sample sizes are small. These results have implications for the design of future interventions targeting WM change.

Is there regional variability in WM changes?

We found that changes in FA, MD, RD, and AD follow the development-to-degeneration spatiotemporal pattern, with greater magnitude of change in the genu of the corpus callosum and the fornix, both late-myelinating regions, as reported in the following studies (Barrick et al.,

2010; Benitez et al., 2018; Burzynska et al., 2017; Hakun et al., 2015; Lövdén et al., 2014; Nicolas et al., 2020; Pfefferbaum et al., 2014; Song et al., 2018; Teipel et al., 2010; Vik et al., 2015). However, in our study, we could not compare the rate of change between the late-and early myelinating regions. Overall, our findings suggest that the fornix and genu of the corpus callosum may be particularly vulnerable to age-related changes.

The fornix is highly vulnerable to vascular deficits and inflammation. Particularly, fornix degeneration appears at preclinical stages of Alzheimer's disease, and it is associated with hippocampal atrophy and progression to Alzheimer's dementia (Lacalle-Aurioles & Iturria-Medina, 2023). Similarly, the genu of the corpus callosum is another WM region susceptible to vascular disease effects and has shown to predict cognitive functioning in patients with mild-cognitive impairment (Raghavan et al., 2020). Future studies should study the impact of within-person change in late-myelinating regions and their role in predicting the progression to neurodegeneration.

In addition, our qualitative review found evidence for the anterior-to-posterior gradient, which was more evident in studies with younger participants (Barrick et al., 2010; Benitez et al., 2018; Teipel et al., 2010; Vik et al., 2015). In contrast, studies examining older adults aged 70 years or older reported changes in FA, MD, and RD in early-myelinating regions (Köhncke et al., 2016; Lövdén et al., 2014; Rieckmann et al., 2016). These findings suggest that within-person changes in adults before age 70 tend to affect late-myelinating fibers. Future studies should further investigate the temporal changes in WM deterioration across late and early myelinating regions in different age groups. This will help us better understand the susceptibility of WM regions in older adults.

What factors modify within-person changes in the WM?

Our review suggests subtle reported effects of aerobic exercise on changes in WM measured with DTI (Burzynska et al., 2017; Voss et al., 2013). This is in line with a previous meta-analysis that found that physical activity was associated with small effects in global measures of WM measured with DTI (Sexton et al., 2016). At the time, the only exercise intervention included was Voss (2013), where aerobic fitness was associated with greater change in WM integrity in the frontal and temporal lobes, with no differences at the group-level.

Similarly, cognitive training was also associated with reduced changes in FA, MD, RD, and AD; however, these results were inconsistent. As discussed above, it is possible that follow-up times shorter than six months are not sufficient to detect within-person changes in WM.

Regarding hypertension and alcohol consumption, the available evidence is limited. To our knowledge, only one study has examined the effects of alcohol consumption patterns as a moderator of within-person changes in WM (Pfefferbaum et al., 2014). Similarly, only a few studies have examined the effect of hypertension and within-person change (Bender, Prindle, et al., 2016; Williams et al., 2019). Given the mixed results and different study designs, more longitudinal studies are needed to draw conclusions about the effects of these moderators.

Genetic polymorphisms such as the APOE ε4 allele have also been shown to moderate within-person changes in WM. Evidence suggests that APOE ε4 carriers show greater within-person change in FA in the corpus callosum, fornix and parahippocampal cingulum (Rieckmann et al., 2016; Williams et al., 2019). Similarly, biomarkers of Alzheimer's disease such as YKL-40 and amyloid-beta burden contribute to greater within-person change in WM (Racine et al., 2019; Song et al., 2018). The effect of amyloid burden was associated with greater within-person change in the fornix (Song et al., 2018). This adds to the evidence that fornix degeneration is associated with a greater risk of Alzheimer's disease (Lacalle-Aurioles & Iturria-Medina, 2023).

Additionally, Raffin et al. (2021) reported an interaction between APOE ε4 status and physical activity in cognitively healthy older adults free of neurological disease. In this study, light physical activity was associated with greater increases in MD and AD among APOE ε4 carriers compared to noncarriers. However, it is important to note that this sample included participants with at least one of the following: spontaneous memory complaints, slow gait speed, or limitation in one instrumental activity of daily living. Therefore, the observed differences between APOE ε4 carriers and noncarriers may be due to differences in health status. Further research is needed to assess whether physical activity may have differential effects on within-person changes in WM depending on genetic risk factors for Alzheimer's disease.

Challenges in Comparing DTI Studies and Heterogeneity

The sources of heterogeneity in the MRI studies included in this meta-analysis may impact the observed effect sizes in within-person changes in white matter DTI over time. One source of heterogeneity is inconsistent reporting. Most studies in this review reported results inconsistently (see Table 3.1 for a summary of reported statistics) and needed to provide important details such as parameter estimates of within-person change or standard deviations of change estimates.

Methodological differences in MRI data can also contribute to heterogeneity. For example, several studies did not calculate DTI values from the TBSS-derived WM skeleton (Charlton et al., 2010; Lövdén et al., 2010; Mielke et al., 2009; Song et al., 2018; Staffaroni et al., 2018; Williams et al., 2019), making their data less comparable with those that derived their WM regions of interest from the standard space skeletonized template derived from TBSS. Two other studies used customized TBSS processing pipelines to derive subject-specific masks from WM atlases deprojected to native space (Bender, Prindle, et al., 2016; Bender, Völkle, et al., 2016). While this method may allow for capturing individual differences in WM microstructure,

it could also result in higher inter-subject variability. Two other studies used a modified TBSS pipeline to account for variation between multiple time points (Coelho et al., 2021; Engvig et al., 2012). They aligned the images taken at different times by computing linear transformations between and resampling them to a common space halfway between the two time points. The initial alignment between the two time points was informed by an extracted skull image, which was assumed not to change over time. This approach has been suggested to improve reliability to detect individual change in longitudinal studies (Madhyastha et al., 2014). Further research is needed to optimize alternative strategies for refining image registration in longitudinal studies.

In contrast, using the traditional TBSS-ROI in standard space has showed excellent precision and reproducibility (Cai et al., 2021). However, TBSS does not guarantee perfect alignment of even major WM tracts (Smith et al., 2006). To reduce misalignments, future studies should carefully inspect image registration results. For structures that are near each other such as the genu and body of the corpus callosum, we recommend checking for potential influence of post-registration misalignments and voxel misassignments. Overall, recommendations for using TBSS include using nonlinear registration techniques or tensor-based group-wise registrations to improve the alignment of tracts. It is also recommended to use a study-specific space (rather than a standard template) for the skeletonization procedure. Additionally, using the default skeleton FA threshold (FA>0.2) and checking stability in regions such as the fornix can improve the accuracy of results. Finally, it is important to adjust for multiple comparisons to control for false positives (Bach et al., 2014).

In our systematic review, we found that 3 studies used tractography (Kocevska, Cremers, et al., 2019; Storsve et al., 2016; Vik et al., 2015) and 1 study used quantitative DTI fiber tracking (Sullivan et al., 2010). Probabilistic tractography methods can have varying degrees of

reproducibility (Maier-Hein et al., 2017). For example, shorter streamlines, truncation effects and seeding strategies can impact the reproducibility and reliability of tractography results (Maier-Hein et al., 2017). New algorithms and seeding strategies have been developed to enhance tractography endpoints near the cortex (St-Onge et al., 2018) and could help to reduce this truncation effect. Re-alignment methods designed to address residual misalignments between subjects can also reduce variability at the group level and should be considered in tractography analysis pipelines (St-Jean et al., 2019). In addition, future innovations that use tighter integration of anatomical priors, advanced diffusion microstructure modeling, and multi-modality imaging should help resolve signal ambiguities and overcome tractography limitations (Maier-Hein et al., 2017).

Lastly, another source of heterogeneity in MRI data could be differences in scanner parameter settings. However, recent multi-site reliability studies have shown that these differences have little impact on DTI analyses (Fox et al., 2012). However, a study with a higher quality of MRI data (60 DWI volumes, *b*-value=1500/s/mm2) suggested that increased quality of the diffusion sequence can lead to higher reproducibility of FA and MD in older adults, in part explained by the number of diffusion-weighted directions, number of b0s images directions, the use of peripheral pulse gating and the quality of the hardware (Luque Laguna et al., 2020). It is possible that the lack of significant within-person changes observed in the first DTI longitudinal studies may be attributed to the lack of standardization in DTI preprocessing pipelines and the lower quality of diffusion sequences (Lövdén et al., 2010; Mielke et al., 2009; Sullivan et al., 2010).

Recommendations for future studies

To improve the accuracy and reliability of future studies on longitudinal within-person changes in WM microstructure, we suggest the following recommendations:

- Future research should use a minimum follow-up time of 6 months to detect significant within-person changes in WM microstructure in healthy adults, especially when sample sizes are small.
- More longitudinal studies should study the effects of potential moderators of within-person change in WM, including aerobic exercise, hypertension, and genetic risk factors.
- Future researchers should strive to standardize reporting and protocols. Standardization includes consistently reporting results and providing important details such as parameter estimates for within-person change in DTI, standard deviations, standard errors, and pre- and post-measurement mean values. Including these details would allow for the calculation of percent change and effect sizes in future meta-analyses.
- Nonlinear registration techniques or tensor-based group-wise registrations could help reduce misalignments of TBSS-derived data. Optimized parameter sets have been published (de Groot et al., 2013) and are described within FNIRT/FSL .
- If using TBSS, it is recommended to use a study-specific space (rather than a standard template) for the skeletonization procedure. Additionally, checking stability in regions such as the fornix can improve the accuracy of results.
- Consider using higher-quality diffusion sequences with more diffusion-weighted directions, number of b0s images directions, and better hardware quality.
- Consider using advanced diffusion microstructure modeling and multi-modality imaging to help resolve ambiguities in the DTI signal.

Future longitudinal studies should expand upon the current findings by using more advanced MRI techniques more sensitive to the WM's microstructural tissue components and water-tissue interactions (Weiskopf et al., 2021). So far only one study used Neurite Orientation Dispersion and Density Imaging (NODDI) to evaluate 15.2-month axonal changes in cognitively healthy adults aged 18-94 (Beck et al., 2021). Incorporating multimodal approaches could provide valuable complementary information among different WM-MRI modalities. For example, using two different neuroimaging techniques (DTI and T1w/T2w ratio), we have shown significant 6-month changes in the WM of cognitively and physically healthy adults of age 60-80 (Burzynska et al., 2017; Mendez Colmenares et al., 2021), suggesting that WM change and decline can be observed in short periods of time. Even though DTI is a strong WM technique to detect age-related decline, the high heterogeneity between studies limited the extend of our conclusions. Future longitudinal studies should aim to use standardized protocols and multiple MRI modalities to improve our understanding of WM changes over time.

3.6. Conclusion

Our study found that WM microstructure undergoes significant within-person changes in older age, as measured with DTI. We found that within-person changes in WM microstructure in healthy older adults predominantly involved declines in FA and increases in MD and RD. The magnitude of change was greater with increasing age and follow-up times. Most studies in this review supported the development-to-degeneration and anterior-to-posterior gradients of WM deterioration. We also found mixed evidence for the effect of sex, hypertension, lifestyle factors, and genetic polymorphisms.

To improve our understanding of WM changes over time and their impact on cognitive aging in healthy adults, as well as Alzheimer's disease and related dementias, future longitudinal

studies should aim to use standardized protocols and multiple MRI modalities. This will enhance the reproducibility of findings and allow for a more comprehensive understanding of the underlying mechanisms of WM change. Ultimately, this will inform the development of targeted interventions to mitigate the effects of cognitive decline in aging and neurodegenerative diseases.

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CHAPTER 4

SYMMETRIC DATA-DRIVEN FUSION OF DIFFUSION TENSOR MRI: AGE DIFFERENCES IN WHITE MATTER

4.1. Overview

In the past 20 years, white matter (WM) microstructure has been studied predominantly using diffusion tensor imaging (DTI). Decreases in fractional anisotropy (FA) and increases in mean (MD) and radial diffusivity (RD) have been consistently reported in healthy aging and neurodegenerative diseases. To date, DTI parameters have been studied individually (e.g., only FA) and separately (i.e., without using the joint information across them). This approach gives limited insights into WM pathology, increases the number of multiple comparisons, and yields inconsistent correlations with cognition.

To take full advantage of the information in a DTI dataset, we present the first application of symmetric fusion to study healthy aging WM. This data-driven approach allows simultaneous examination of age differences in all four DTI parameters. We used multiset canonical correlation analysis with joint independent component analysis (mCCA+jICA) in cognitively healthy adults (age 20–33, n=51 and age 60–79, n=170). 4-way mCCA+jICA yielded one high-stability modality-shared component with co-variant patterns of age differences in RD and AD in the corpus callosum, internal capsule, and prefrontal WM. The mixing coefficients (or loading parameters) showed correlations with processing speed and fluid abilities that were not detected by unimodal analyses. In sum, mCCA+jICA allows data-driven identification of cognitively relevant multimodal components within the WM. The presented method should be further extended to clinical samples and other MR techniques (e.g., myelin water imaging) to test the

potential of mCCA+jICA to discriminate between different WM disease etiologies and improve the diagnostic classification of WM diseases.

4.2. Introduction

Degradation in myelin and axonal structure in the white matter (WM) is one of the fundamental mechanisms contributing to cognitive decline in normative aging and Alzheimer's Disease and Related Dementias (Nasrabady et al., 2018). However, *in vivo* age differences in WM microstructure mechanisms are only partially understood. This is because almost all neuroimaging studies on the WM microstructure in aging in the past 20 years have used diffusion MRI and, predominantly, diffusion tensor imaging (DTI)(Madden et al., 2012).

Fractional anisotropy (FA) is a measure of the directional dependence of diffusion (Pierpaoli & Basser, 1996) and is influenced by the fiber orientational coherence, fiber diameter, integrity, and density (Beaulieu, 2002). Mean diffusivity (MD) reflects the total magnitude of diffusion within a voxel, which is inversely proportional to the density of physical obstructions, such as myelin and cellular membranes (Beaulieu, 2002; Sen & Basser, 2005). Radial diffusivity (RD) measures the magnitude of diffusion perpendicular to the primary orientation of WM tracts, which in WM is restricted by axonal and myelin membranes. Axial diffusivity (AD) is a measure of diffusion along the length of an axon and is thought to reflect chronic axonal injury. RD and AD have been linked to axonal damage and loss in myelin membrane integrity (Sun et al., 2008; Winklewski et al., 2018). Notably, AD and RD are orthogonal, and FA and MD are mathematical combinations of AD and RD. However, it is important to keep in mind that DTI measures are only proxies for WM microstructural integrity and are not specific to any underlying neurobiological mechanism (Jones et al., 2013). Decreased FA and increased MD,

RD, and bidirectional differences in AD have been consistently reported in healthy aging and Alzheimer's Disease and related dementias (Nir et al., 2013).

Importantly, most DTI studies on aging and dementia have used only a fraction of information available in a diffusion dataset. Typically, age differences have been reported either selectively (e.g., only FA), in arbitrarily selected regions (e.g., the corpus callosum), and separately (i.e., without using the joint information across them, for example, shared versus unique information across FA and RD). Therefore, the aim of this study was to evaluate the use of the joint information across all four DTI parameters to revisit age differences in the entire WM using a data-driven symmetric fusion analysis.

There are different types of multimodal analysis (Calhoun & Sui, 2016). At one end of the spectrum is the visual inspection of different data types. For example, the analysis of the spatial overlap of unimodal analyses. We have used this approach in our earlier work, attempting to delineate different microstructural mechanisms of WM aging from overlapping patterns of age differences in FA, MD, RD, and AD (Burzynska et al., 2010). However, the overlap of voxels showing significant differences in each parameter map does not measure the interaction among them. As a result, our interpretation of the patterns of WM aging remained inconclusive.

In the current study, we use data fusion on the opposite side of the spectrum, namely, symmetric data fusion, which treats multiple image types (or modalities) equally to take full advantage of their joint information (Calhoun & Adali, 2009; Calhoun & Sui, 2016). We chose to use data-driven multiset canonical correlation analysis with joint independent component analysis (mCCA+jICA) (Calhoun & Sui, 2016; Sui et al., 2018; Sui, He, Pearlson, et al., 2013). This method combines the flexibility of mCCA in maximizing covariations between the

modalities (Correa et al., 2008) with superior source separation with jICA (Sui, He, Pearlson, et al., 2013).

mCCA+jICA outputs modality-shared and modality-unique independent components (IC). These ICs represent sources of the signal, which – we hypothesize, based on unimodal analyses of DTI data – should be congruent with age-related processes in WM microstructure known from histological studies. For example, a modality-shared IC composed of decreased FA and increased MD, RD, and AD in older adults would likely reflect demyelination or chronic tissue loss (Burzynska et al., 2010; Mac Donald et al., 2007; Winklewski et al., 2018). The retrogenesis hypothesis of brain aging (Brickman et al., 2012) posits that WM regions that are last to myelinate during development are also most vulnerable to aging. Thus, we hypothesized that an IC reflecting demyelination or tissue loss would be localized predominantly to late-myelinating WM regions, such as the prefrontal WM, anterior corpus callosum, fornix, and the external capsule (Dean et al., 2017; Kinney & Volpe, 2018; Slater et al., 2019).

Next, with this data-driven, exploratory approach, we expected to obtain new insights into age differences in WM microstructure that cannot be identified with a single parameter map or image modality or by using traditional inferential statistics. Multimodal analyses using partial least squares (Konukoglu et al., 2016) or linked ICA (Doan et al., 2017) showed great promise in identifying patterns of correlated group differences across diffusion MRI features to improve diagnostic classification between healthy controls and people at different stages of Alzheimer's disease.

Finally, to date, unimodal analyses yielded mixed associations with cognition, with marked inconsistencies between WM regions or tracts, DTI parameters, and cognitive constructs, possibly hampered by the number of multiple comparisons (Kennedy & Raz, 2009a; Madden et

al., 2012; Sasson et al., 2013). Therefore, we aimed to test whether multimodal fusion can identify components relevant to cognition. Specifically, we hypothesized that covariant DTI differences between young and old would be associated with executive functions and processing speed, the cognitive functions most affected by aging and possibly most sensitive to changes in brain's structural connectivity via WM (Sullivan et al., 2010).

4.3. Methods

Participants

The MRI data used in this study were obtained from three studies conducted between 2011 and 2014 on neurologically and cognitively healthy adults. We acquired the data using the 3T Siemens TIM Trio system with 45 mT/m gradients and 200 T/m/sec slew rates (Siemens, Erlangen, Germany) at the Beckman Institute for Advanced Science and Technology at the University of Illinois, USA. All studies were approved by the University of Illinois at Urbana-Champaign Institutional Review Board, with written informed consent obtained from all participants.

Older Adults: Data for older adults was obtained from the baseline MRI data of community-dwelling participants (n=170), aged 60-79 years, in the Fit and Active Senior clinical trial (ID: NCT01472744). For more information, refer to (Baniqued et al., 2018; Burzynska, Jiao, et al., 2017; Ehlers et al., 2016, 2017; Fanning et al., 2016; Mendez Colmenares et al., 2021; Voss et al., 2018).

Young Adults: Data for young adults was collected in two separate studies. The first study included n=37 female dancers (aged 18-33) and education-matched peers with no professional dance training, recruited from the student population at the University of Illinois

(Burzynska, Finc, et al., 2017). The second study comprised n=14 college-age young adults, collected as a reference sample for the FAST clinical trial.

Our final sample consisted of 221 participants (n=51 young and n=170 older adults; see Figure A.4 for participant flow).

DTI

DTI images were obtained with no interslice gap, with a twice-refocused spin echo single-shot Echo Planar Imaging sequence (Reese et al., 2003) to minimize eddy current-induced image distortions. The protocol consisted of a set of 30 non-collinear diffusion-weighted acquisitions with *b*-value = 1,000 s/mm^2 and two T2-weighted *b*-value = 0 s/mm^2 acquisitions, repeated two times, with 128 × 128 matrix, GRAPPA acceleration factor 2, flip angle = 90, and a bandwidth of 1698 Hz/Px. The DTI acquisition for the young dancer sample differed slightly on voxel dimensions and field of view (TR/TE = 10000/98 ms, 1.9 × 1.9 mm^2 in-plane resolution, and 72 2-mm-thick slices for full brain coverage), from the other young and older samples (TR/TE = 5,500/98 ms, 1.7 × 1.7 mm^2 in-plane resolution, and 40 3-mm-thick slices). DTI data were processed using the FSL Diffusion Toolbox v.3.0 (FDT: http://www.fmrib.ox.ac.uk/fsl) (Burzynska et al., 2017). We used the TBSS (Tract-Based Spatial Statistics workflow (Smith et al., 2006) to align diffusion images into a 1x1x1mm standard Montreal Neurological Institute (MNI152) space via the FMRIB58_FA template and project the center-of-tract values onto the WM skeleton. Our final sample consisted of 221 participants (n=51 young and n=170 older adults).

Symmetric data fusion (mCCA+jICA)

Multimodal age comparative analyses were carried out using a 4-way (FA, MD, RD and AD) two-sample t-test mCCA+jICA (Calhoun, Adali, Giuliani, et al., 2006; Calhoun & Sui, 2016; Sui et al., 2018; Sui, He, Pearlson, et al., 2013) using the Fusion ICA MATLAB Toolbox

(http://trendscenter.org/software/fit/) as described in Figure 4.1. We restricted our analyses to the WM skeleton thresholded at the default FA > 0.2.

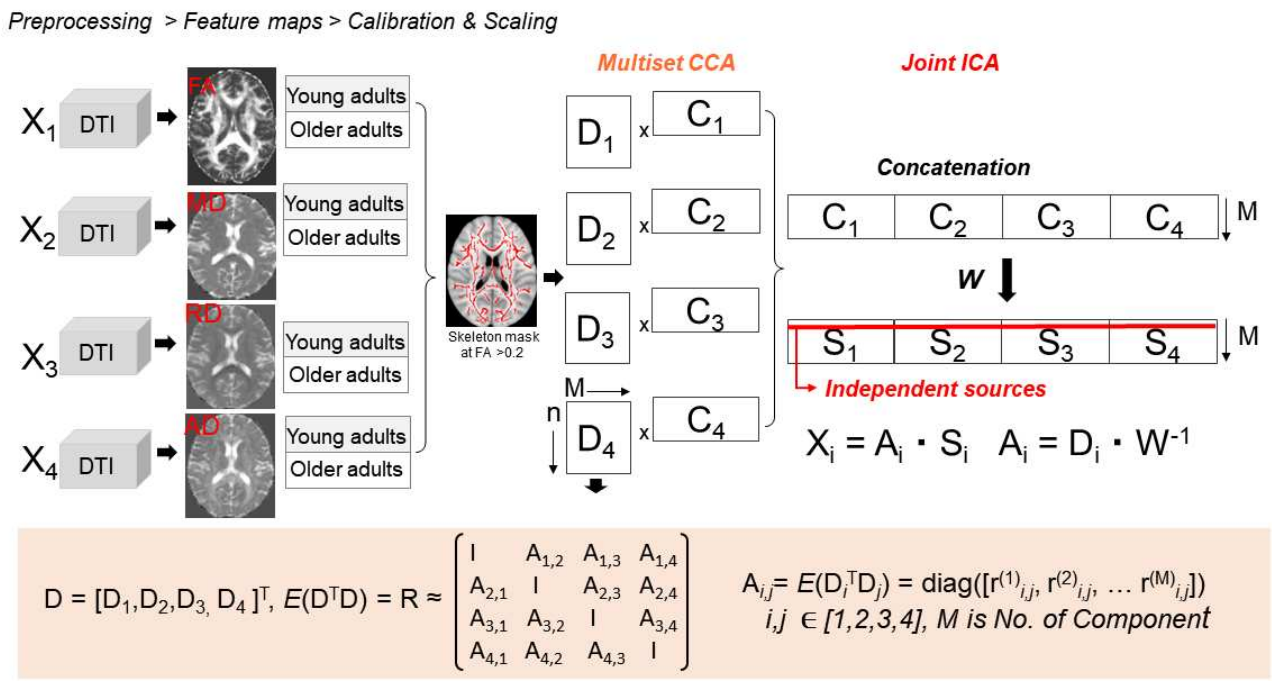

Figure 4.1
4-way 2-samples t-test mCCA+jICA. mCCA projects the data in a space so that the correlations among mixing profiles (D_k, k=1…n) of the four parameter maps are jointly maximized, resulting in canonical variates. Analyses were restricted to the WM using a TBSS-derived skeleton WM mask. D_k is then sorted by correlation to provide a closer initial match and make the further application of joint ICA more reliable. Joint ICA is then applied on the concatenated maps [C_n] to obtain the final independent sources

Model order

There are several ways of selecting the optimal model order (i.e., the number of resulting ICs), ranging from *a priori* to data-driven methods. Currently, there is no gold standard for selecting the model order for mCCA+jICA for exploring specifically skeletonized WM space. Therefore, to select our model order, we used *a priori* knowledge from postmortem histological examinations in humans and primates (Aboitiz et al., 1996; Marner et al., 2003; Mason et al.,

2001; Meier-Ruge et al., 1992; Peters, 2002; Tang & Nyengaard, 1997; Tse & Herrup, 2017) as well as from spatial patterns of overlap in age differences in FA, MD, RD and AD identified in earlier cross-sectional DTI studies (e.g. (Bennett et al., 2009; Burzynska et al., 2010)). The known histological age differences in WM include: 1) loss or thinning of myelin, 2) decrease in average axonal diameter, 3) loss of whole myelinated axons that may be associated with 4) decrease in tissue density and increase in extracellular (free) water or 5) increase in cellular density due to gliosis. Other histological changes in the aging WM include changes in axonal orientational alignment in a voxel due to 6) loss or rarefaction of fibers in a specific direction or 7) realignment due to macrostructural changes, as well as 8) changes in the microvasculature. Thus, we decided that a model with 8 ICs would provide enough flexibility to accommodate a broad of possible microstructural processes yet be low enough to accommodate the restricted space of the WM skeleton (~8% of the total brain volume).

IC quality assessment

We used 500 random iterations of ICA using the entropy-based minimization ICA (EBM ICA) algorithm (Du et al., 2011). We used ICASSO to select the best single-run estimate to ensure the replicability of our results (Du et al., 2014). ICASSO runs the ICA algorithm repeatedly and compares each result based on the correlation between squared source estimates (Himberg & Hyvärinen, 2003). Next, ICASSO estimates the stability of the ICA using clustering analysis to compute a cluster quality index, Iq. We defined the Iq as ($I=avg(S(i)_{int})-avg(s(i)_{ext})$, where S is the spatial similarity between two ICs and i is the source matrix. Therefore, the Iq value represents the difference between intra- and inter-cluster component similarity. We used the quality index to assess the stability and reliability of the resulting ICs. Most studies use a

quality index threshold between 80-90% (Gholamipour & Ghassemi, 2021; Hirjak et al., 2019; Malhi et al., 2019; Naveau et al., 2012); thus, we chose to examine only the ICs with an Iq>0.90.

mCCA+jICA

When applying the mCCA+jICA model, the 3D data were first reshaped to a one-dimensional vector by subject. Then, the data were normalized separately for each data type, ensuring that each data type has the same average sum of squares, which is computed across all subjects and voxels. This normalization process ensures that all features have the same ranges and contribute equally to the fusion model (Calhoun, Adali, Kiehl, et al., 2006) (Fig. 4.1). After running ICASSO, mCCA+jICA outputs a source matrix (loadings for each voxel) and a mixing matrix (loading coefficients for each component for each subject) (Hirjak et al., 2019). The mixing matrix allows for analyzing the inter-correlation between modalities and the differences between the groups (young vs. old). Therefore, modality-shared ICs (with significant mixing coefficients in at least two modalities) share variance across at least two feature maps, while modality-unique ICs represent unique variance. The mixing coefficients (also called loading parameters) reflect the degree to which a given component is expressed in each subject for a given feature. We used the GIFT Toolbox (https://trendscenter.org/software/gift/) to plot the mixing coefficients in MATLAB. To visualize each independent component, each source matrix was reshaped to a 3D space, standardized (z-scored), and thresholded at z>2.5 (p<0.01, two-tailed). We tested the hypotheses by analyzing the composition, spatial location, and direction of age differences in the ICs. The composition of each IC is determined by the mixing coefficients and p-values associated with its feature maps.

Cognitive assessment

Cognitive assessment included the Virginia Cognitive Aging (VCAP) battery (Salthouse, 2009) administered as described in (Mendez Colmenares et al., 2021). Two cognitive composites were used in the analyses due to their reliance on WM integrity (Madden et al., 2012): executive function (matrix reasoning, Shipley abstraction, letter sets, spatial relations, paper folding, and form boards) and perceptual speed construct (digit symbol substitution, letter comparison, pattern comparison). We calculated the composites as a sum of the z-score values across the respective tasks. Two subjects were missing data from all cognitive scores; these two subjects were included in the fusion analyses but not in the regression analyses with cognition. An additional five subjects were missing data for the "Letter Sets task" and two had missing data for the "Form Boards task" due to technical issues. For these seven subjects with missing data from one task, we replaced the missing score with the sample mean when calculating the composite scores, resulting in $n = 219$ for the final cognitive analyses.

Statistics

The regression analysis between the mixing coefficients and cognition was corrected for family-wise error using the false discovery rate (FDR) method as implemented by p.adjust in R. We created figures using the ggplot function in the ggplot2 package (Wickham, 2016). We performed statistical analyses in R version 4.2.1. Lastly, to minimize the effects of the outliers but to avoid removing data points, for both the mixing coefficients and the cognitive composites we identified outliers as < 1st percentile or > 99th percentile of distribution (i.e., winsorized) by replacing them with the nearest value in the 1st or 99th percentile.

4.4. Results

Sample characteristics

The older and younger adults in our sample showed the expected age difference in speed and fluid abilities, as well as whole-skeleton DTI values, but did not differ on education. Additionally, the young adult group had a higher proportion of females than the older adult group (Table 4.1).

Table 4.1

Sample characteristics

Variables	Young n=51	Old n=170	*p* value
Age	21.6±3.2	65.4±4.4	0.001
Women, n (%)	47 (91)	117 (68)	0.001
Education, years	15.4±2.2	15.8±2.9	0.409
DTI parameters			
FA	0.479±0.02	0.454±0.01	0.001
MD	0.753±0.01	0.767±0.03	0.001
RD	0.586±0.09	0.507±0.16	0.001
AD	0.661±0.21	1.126±0.09	0.001
Cognitive scores			
Digit symbol	82.96±26.96	65.39±13.79	0.001
Pattern Comparison	19.05±4.31	14.82±2.57	0.001
Letter Comparison	12.45±2.94	9.53±1.82	0.001
Letter Sets	12.54±2.09	11.05±2.69	0.001
Spatial relations	12.05±4.92	8.08 ±4.73	0.001
Paper folding	8.57±3.29	5.42±2.57	0.001
Form boards	9.88±4.41	5.60±3.69	0.001
Shipley Abstract	15.20±2.58	12.36±3.55	0.001
Matrix Reasoning	11.49±3.23	8.12±3.03	0.001

Note. MD, RD, and AD are expressed in μm2.ms−1. Values are presented as mean ± standard deviation unless otherwise stated.

mCCA+ICA output

Among the eight ICs, only one (IC2) had a qualifying Iq=.923. IC2 was a multimodal component with RD and AD showing significant age-discriminatory contributions. As shown in Figure 4.2, RD showed an increase in older adults in the right anterior and posterior internal

capsule, body, and splenium of the corpus callosum, in the occipital WM, prefrontal WM and frontal WM (anterior corona radiata and anterior cingulate) (voxels in red). RD was decreased in older adults in fewer regions, which included the left anterior and posterior capsule, genu, and splenium corpus callosum (voxels in blue). AD was mostly decreased in older adults, which included the corpus callosum genu and splenium, right internal capsule, and prefrontal WM (blue). AD was increased in the older adults in a cluster of the left internal capsule and scattered voxels in the forceps minor and major (red).

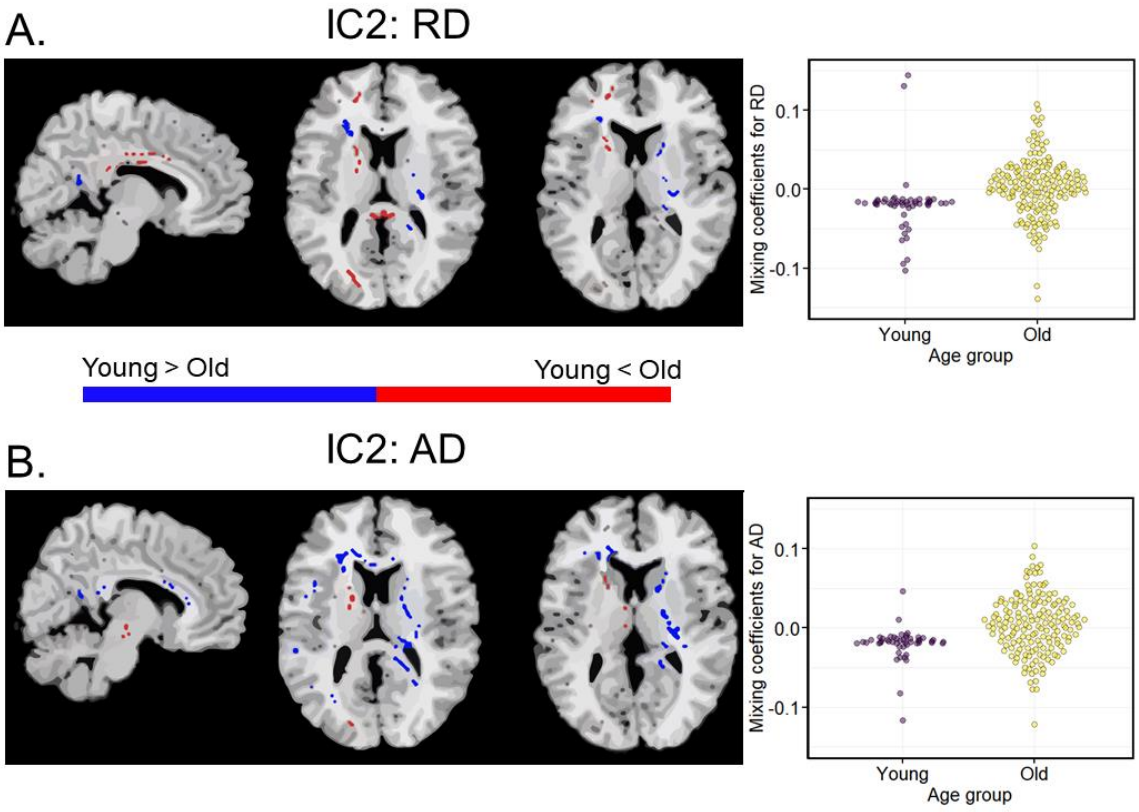

Figure 4.2
A modality-shared independent component (IC2) differentiating younger and older adults via independent samples t-test on mixing coefficients. A. Spatial maps for RD. B. Spatial maps for AD. When z scores (red voxels) are positive and mixing coefficients are positive, the component is showing increased RD/AD in older adults. Conversely, when z-scores are negative (blue voxels) and mixing coefficients are positive, the component is showing increased RD/AD in young adults. Density plots show the loading parameters (or mixing coefficients) of IC2 for both RD and AD feature maps. Higher mixing coefficients for both RD and AD in older adults mean

that IC2 was expressed more in older adults. All the two-sample t-tests between young and older adults had $p<0.01$. IC: independent component.

Mixing coefficients and cognition

To test whether the age differences in RD and AD depicted by IC2 were relevant for cognition, we conducted regression analyses to examine the relationship between the mixing coefficients for RD and AD and the executive function and processing speed composites. Because both DTI values and cognition show strong associations with age, which may drive their correlation (Burzynska et al., 2010, 2020), we residualized the executive function and processing speed controlling for age. Note that the mixing coefficients for RD and AD already contain age information, so they were not residualized. The scatterplots in Figure 4.3 display the relationship between the mixing coefficients and cognitive scores, while controlling for sex and education. The regression lines represent the results of the linear models fitted to the data. After controlling for these covariates and correcting for multiple comparisons, we found that higher mixing coefficients for RD and AD were associated with better executive functioning and processing speed.

To test whether the IC2-cognition association was present in both younger and older groups, we performed regression analyses by age group, adjusting for sex and education (Table 4.2). We found that the mixing coefficients for RD and AD were significant predictors of executive function and processing speed only among older adults but not among younger adults. In the older group, in addition to the mixing coefficients, education was a significant positive predictor of executive function and processing speed.

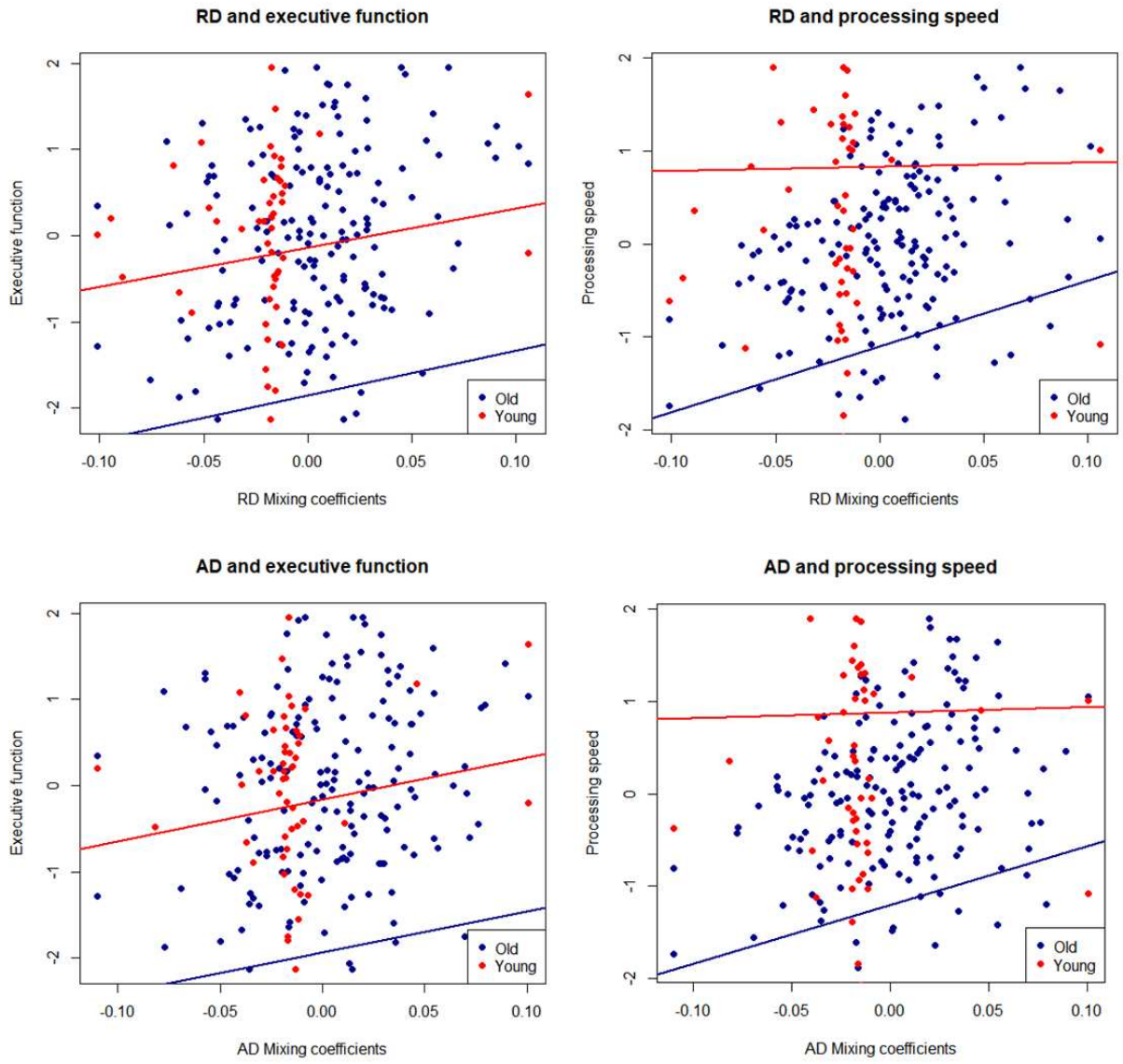

Figure 4.3

Mixing coefficients for IC2- RD and IC2- AD and association with executive function and speed composites. Lines of fit are adjusted by sex and education. Cognitive scores are residualized for age.

Table 4.2

Regression analyses of mixing coefficients for RD and AD as predictors of executive function and processing speed

	Executive Function						Processing Speed					
	Young			Old			Young			Old		
	β	*p*	*q*	*β*	*p*	*q*	*β*	*p*	*q*	*β*	*p*	*q*
Model 1												
IC2- RD	0.110	0.442	0.530	0.186	0.010	0.004	0.009	0.921	0.980	0.321	0.001	0.003
Education	0.155	0.328	0.437	0.350	0.001	0.006	-0.271	0.013	0.026	0.272	0.001	0.003
Sex	0.760	0.202	0.404	-0.027	0.818	0.884	-0.010	0.980	0.980	0.154	0.091	0.156
Model 2												
IC2 -AD	0.142	0.319	0.437	0.173	0.017	0.051	0.014	0.880	0.980	0.291	0.001	0.003
Education	0.155	0.139	0.333	0.363	0.001	0.006	-0.272	0.013	0.026	0.292	0.001	0.003
Sex	0.663	0.254	0.435	0.023	0.884	0.884	-0.010	0.972	0.980	-0.172	0.272	0.408

Table 4.2 displays the results of regression analyses examining the relationship between mixing coefficients for radial diffusivity (RD) and axial diffusivity (AD) and executive function and processing speed among young and old adults. Sex is coded as 0=female, 1=male. β are standardized coefficients. Model 1 includes RD mixing coefficients, education (years), and sex. Model 2 includes AD mixing coefficients, education (years), and sex. P-values (*p*) were corrected for multiple comparisons using the FDR method, denoted as "*q*".

The fundamental question we were interested in answering is whether the multimodal fusion of DTI parameters using mCCA+ICA would provide more relevant information on age differences in WM concerning cognition than conventional, unimodal analysis. To investigate this, we conducted regression analyses between mean FA, MD, AD, and RD across the whole WM skeleton with executive function and perceptual speed scores, controlling for age, sex, and education. No association was significant after FDR correction. See Table A.4. for more details.

4.5. Discussion

We present the first application of symmetric multimodal fusion analysis, mCCA+jICA, to characterize joint age differences in four DTI feature maps: FA, MD, AD, and RD, in only WM space. Our analyses revealed one high-stability modality-shared IC with co-variate patterns of RD and AD that differentiated between young and older adults. The joint information across RD and AD showed a superior association with cognitive performance compared to unimodal analyses.

Joint differences in DTI parameters between young and older adults

In the context of our study, we can interpret the mixing coefficients as the strength of the covariance between the DTI features in expressing age differences in the WM microstructure for each IC. In other words, a higher mixing coefficient for RD and AD indicated stronger age differences in RD and AD in the regions indicated in IC-2. There are a couple of observations that we would like to highlight when interpreting mixing coefficients.

First, the variance in the mixing coefficients was greater in the old group than in the young group, consistent with age-related increases in heterogeneity, as previously described for other structural and functional brain features (Dennis & Cabeza, 2011; Koen & Rugg, 2019). Second, we found more negative values of mixing coefficients in older participants, suggesting weaker associations between RD and AD within the IC2. It is possible that the negative mixing coefficients observed in older adults reflect a decrease in the spatial specificity of WM microstructures with age, in line with the dedifferentiation hypothesis, which posits that certain neural processes become less distinct and spatially specific with age (Koen & Rugg, 2019). In this context, this could reflect an increased variability in the extent and localization of myelin loss or other histological processes. However, this possibility needs to be investigated by fusing

features generated with MRI methods specific to myelin and axonal components such as myelin water fraction, neurite density orientation, and quantitative magnetization transfer (Faizy et al., 2018; Gatto et al., 2018; Jelescu et al., 2016). Additionally, it is worth noting that the results observed in the young group might be influenced by a restriction of range in the data, which could potentially affect the interpretation of the linear regression model results. Further investigation is needed to confirm and understand the implications of this limitation.

Overall, the results from the mCCA+jICA approach demonstrate a unique pattern of joint age differences in RD and AD. Modality-shared IC2 was localized to the splenium of the corpus callosum, internal capsule, and prefrontal WM. The genu of the corpus callosum is the primary late-myelinating WM region, achieving peak myelination ~70-109 weeks after birth (Kinney & Volpe, 2018). Related to this, it is characterized by small axon diameter, thin myelin sheaths, and a low oligodendrocyte-to-axon ratio, which makes its myelin sheaths metabolically challenged and more vulnerable to age-related deterioration (Bartzokis et al., 2004). The splenium of the corpus callosum is also considered late-myelinating, with peak myelination achieved ~68 weeks after birth. The anterior internal capsule also has peak myelination achieved ~109 weeks after birth. In contrast, the posterior internal capsule is considered early-myelinating and begins myelinating <68 weeks before birth. Thus, our results support the retrogenesis pattern of WM degeneration, except for the voxels in the posterior internal capsule.

As known from unimodal analyses, age differences are typically characterized by decreased FA, increased MD and RD, and bidirectional differences in AD (Bennett et al., 2009; Burzynska et al., 2010; Kennedy & Raz, 2009b). In contrast, the mCCA+jICA showed no age differences in FA or MD, but rather a covariation of age bidirectional differences in RD and AD. However, the increases in RD were mostly localized to the genu of the corpus callosum,

prefrontal WM and anterior limb of the internal capsule, consistent with the retrogenesis hypothesis and vulnerability of myelin in late-myelinating regions.

We observed that increases in RD in the splenium of the corpus callosum and prefrontal/frontal WM were accompanied by lowered AD in the same regions. Studies using DTI-post-free water elimination have revealed that increases in RD accompany a decrease in AD with age, for example, in the frontal WM and parts of the corticospinal tracts (e.g., superior corona radiata) (Chad et al., 2018). Our earlier work also showed that increases in RD were accompanied by a decrease in AD in the superior corona radiata and prefrontal WM regions, but this effect was accompanied by decreased FA (Burzynska et al., 2010). Our study suggests that mCCA+jICA allows the detection of unique age differences driven by RD and AD independently of FA and MD.

In summary, mCCA+jICA is sensitive to the cross-information among all DTI features, which captures how DTI features interact and creates independent sources that explain unique mechanisms of WM aging (Calhoun & Sui, 2016). This multimodal fusion approach allowed us to revisit age differences in the entire WM using a data-driven approach. As hypothesized, this IC showed co-variant age differences in RD and AD in late-myelinating regions that may reflect demyelination, unrestricted diffusion of water –or chronic axonal loss (Klawiter et al., 2011; Underhill et al., 2009). Future studies should extend these results and test the utility of multimodal fusion using quantitative MR features with greater specificity for WM microstructure.

Ability to detect age differences relevant to cognition

Associations of DTI with cognition (Madden et al., 2012) have been inconsistent, possibly due to multiple factors such as selective DTI parameter use, selective ROI, or type II

error caused by multiple comparisons. We showed that mCCA+jICA could detect co-varying patterns of RD and AD that show a superior correlation with cognition than unimodal analyses, emphasizing the importance of studying WM MRI modalities together.

This first application of mCCA+jICA to study age differences in healthy aging WM identified multimodal patterns linked to executive function and processing speed composite scores. Specifically, RD-AD IC2 positively correlated with processing speed and executive function among the older adults, suggesting that RD and AD shared co-variance may capture a more nuanced pattern of age-related WM differences that correlates with cognition more robustly than any DTI feature alone.

The regression analyses indicated that education also had a positive effect on cognition among the older adults, which is consistent with the cognitive reserve theory (Stern, 2009). The fact that this positive effect was observed only in the older group may reflect a cumulative effect of past educational experiences, subsequent socioeconomic status, and environmental enrichment among older adults. In younger adults, this association may be more obscured given that the highest level of education determines peak cognitive performance and the age of maximal cognitive functioning (Guerra-Carrillo et al., 2017), and that many of our younger participants were still continuing their education.

While our results showed a superior correlation with cognition compared to unimodal analyses, our multimodal fusion approach does not maximize both the inter-modality associations and the correlations with cognition. An extension of mCCA+jICA, mCCA+jICA with reference uses a supervised multimodal approach to maximize the correlation between cognitive scores and mixing coefficients (Qi et al., 2018). This supervised fusion approach can extract IC associated with a specific prior reference (e.g., cognitive scores) to optimize the

decomposition of components and maximize the correlations with cognition. Future multimodal fusion studies should integrate mCCA+jICA and mCCA+jICA with reference to further study the patterns of WM aging, as well as the role of WM in key models of neurocognitive aging such as compensation (Cabeza et al., 2018), neural efficiency (Deary et al., 2010; Penke et al., 2012), or dedifferentiation (Koen & Rugg, 2019).

Technical considerations and limitations

We need to consider several strengths and limitations in interpreting our results. First, we used the ICASSO algorithm to run multiple iterations of ICA and select the best single-run estimate to ensure the replicability of our results (Du et al., 2014). This approach generates more reliable estimates for an IC than an estimate from a single run of the ICA algorithm (Himberg & Hyvärinen, 2003). Since ICA algorithms (indeed most machine learning algorithms) are often stochastic in nature, replication requires addressing this aspect (Adali & Calhoun, 2022). Here we wanted to quantify the reliability of our ICA estimates to acquire more stable results. Currently, there are different strategies to evaluate the reliability of ICs using distinct clustering algorithms, including ICASSO. However, there are no current studies to establish the use of other measures of replicability/reliability of ICA results in DTI datasets, as most fusion models involve fMRI and EEG datasets (Gholamipour & Ghassemi, 2021; Wei et al., 2022). Consequently, we chose a stricter quality index threshold from ICASSO to assess component stability. Future studies should explore using ICASSO and other clustering algorithms to estimate the stability of ICA components in DTI datasets.

Second, the four DTI parameters are based on the same diffusion tensor. These parameters can provide some unique information about tissue diffusivity; however, some microstructural processes in the WM present distinct patterns and combinations of increased/decreased FA, MD, RD, and AD (Burzynska et al., 2010). Thus, by fusing all four DTI

parameter maps and maximizing the information from each DTI feature, we aimed to overcome — at least to some extent — the lack of specificity and mitigate the potential collinearity across the parameters. The mCCA+jICA model assumes some degree of correlation across modalities but allows accurate source separation based on the initial correlation between mixing profiles. In addition, mCCA+jICA has shown high accuracy in estimating independent sources, especially among sources derived from mixing profiles with distinct canonical correlation coefficients (Sui et al., 2012).

Another limitation is that DTI parameters reflect biological processes that depend on tissue architecture (e.g., in regions with crossing fibers). Because DTI confounds integrity, density, the diameter of myelin and axons, fiber orientational coherence, and the volume fraction of extracellular water (Alexander et al., 2007; Jones et al., 2013; Jones & Cercignani, 2010), DTI alone may not be enough to study the aging WM. Future studies should attempt fusing modalities with greater sensitivity and specificity to myelin or axons, such as myelin water fraction, neurite density orientation, and quantitative magnetization transfer (Faizy et al., 2018; Gatto et al., 2018; Jelescu et al., 2016).

In addition, we used a model order of 8 ICs, which is lower than the order of 12–15, typically used in mCCA+jICA analyses that include whole-brain data (Hirjak et al., 2019; Sui, He, Yu, et al., 2013). However, given that the WM skeleton occupies only ~8% of the total brain volume (137.832 skeleton voxels divided by 1.827.095 voxels of full-brain FA map in MNI space) in a sheath-like-structure and that structural data should exhibit fewer patterns that functional data, we concluded that eight ICs should provide enough flexibility in modeling age differences in WM. Although using the TBSS skeleton minimizes the effects of partial volume on DTI parameter values (Metzler-Baddeley et al., 2012) in samples with a broad age span, it

results in the data having a sheath-like structure, which may affect the component structure. We chose the TBSS approach for our study as it allows for representing local WM voxels and restricts the analyses to the center of WM tracts, reducing contribution from partial volume and white matter hyperintensities. Using skeletonized data at a 0.2 threshold also reduces the multiple comparisons problem and increases statistical power. While an ROI approach is typically preferred for confirmatory analyses, it would not be suited for mCCA+jICA which requires one continuous set of voxels for identifying patterns.

Lastly, because methods to estimate the number of components in data fusion have been developed using fMRI and EEG datasets (Akhonda et al., 2021), we estimated the number of components based on *a priori* knowledge of mechanisms of WM aging. As a result, we included the ICASSO algorithm in the mCCA+jICA framework to evaluate our components' robustness and reliability carefully.

4.6. Conclusions

Together, symmetric multimodal fusion a) can provide new and potentially more rigorous information about brain aging, b) can identify age differences in WM that bear more relevance to cognition than those obtained with traditional, region-based unimodal approaches. However, the DTI model, especially with a unimodal approach, provides limited information about the underlying neurobiological mechanisms of aging and dementia. Future multimodal fusion analyses should include more advanced MRI techniques sensitive to the WM's microstructural tissue components and water-tissue interactions (Weiskopf et al., 2021). Multimodal approaches allow leveraging the complementary information among different MRI modalities, representing an opportunity to characterize the role of WM connectivity in cognitive dysfunction and dementia.

4.7. References

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CHAPTER 5

5.1. Conclusions

This dissertation provides valuable insights into the dynamic nature of white matter in healthy aging, exploring white matter decline and plasticity through the application of innovative techniques and analytical approaches. The three manuscripts presented in this thesis contribute to a more comprehensive understanding of the underlying neural processes contributing to age-related cognitive decline and further extend our knowledge of current theories of white matter aging.

The first manuscript provides evidence for experience-induced plasticity in aging white matter through an aerobic walking and dance randomized controlled trial. Our findings suggest that the adult brain maintains plasticity in regions vulnerable to aging, such as the anterior corpus callosum, and can be stimulated even in older adults. This study supports the retrogenesis hypothesis, which suggests that the regions of the white matter that continue to change during our lives and adapt to our experiences may be vulnerable to age-related decline and plasticity. This study also demonstrates the potential of the T1w/T2w signal as a useful and broadly accessible measure for studying short-term within-person plasticity and deterioration in adult human white matter. Future studies are needed to understand the exercise-induced adaptations leading to increased T1w/T2w and their effects on episodic memory.

The second manuscript demonstrates that white matter microstructure undergoes significant within-person changes in older age, with FA declines and MD and RD increases. The magnitude of change increases with advancing age and supports the retrogenesis hypothesis and anterior-to-posterior gradients of white matter deterioration since we found that late-myelinating regions like the fornix and the genu of the corpus callosum were more vulnerable to within-

person changes. The study also analyzed data from multiple longitudinal studies and found that older age, female sex, and longer time until follow-up were associated with greater declines in FA in the whole white matter. This systematic review and meta-analysis provide recommendations for future longitudinal studies and highlight the importance of using standardized protocols and multiple MRI modalities to inform further the development of targeted interventions to mitigate the effects of white matter decline.

The third manuscript introduces the first application of symmetric fusion to study healthy aging white matter, using multiset canonical correlation analysis with joint independent component analysis (mCCA+jICA). This data-driven approach allowed us to examine age differences in the white matter using four different DTI features, taking advantage of the joint information across all features. Further, this multimodal fusion approach identified age differences in white matter that showed more relevance to cognition than those obtained with traditional, region-based unimodal approaches. This study demonstrates the potential of multimodal fusion approaches to characterize the role of white matter connectivity in cognitive decline by leveraging complementary information among different MRI types.

Together, this dissertation contributes to a deeper understanding of white matter changes over time in the aging brain. This work contributes to future studies developing effective interventions targeted at white matter to promote healthy brain aging. Future studies should continue to leverage multimodal approaches to provide a more comprehensive understanding of the role of white matter connectivity in age-related cognitive decline and Alzheimer's disease and related dementias. Future studies should also extend our findings using more advanced MRI modalities with greater sensitivity and specificity to myelin or axons, such as myelin water fraction, neurite density orientation, and quantitative magnetization transfer (Faizy et al., 2018;

Lee et al., 2020; Zhang et al., 2012).

5.2. Significance

Using a novel white matter measure, the standardized T1w/T2w, the first manuscript of this dissertation provided the first evidence of plasticity induced by a 6-month exercise intervention in vulnerable white matter regions in healthy older adults (Mendez Colmenares et al., 2021). Our findings suggest that white matter retains some degree of plasticity in regions known to be vulnerable to aging and that exercise-induced changes in these regions may translate to improved episodic memory. This is significant because white matter changes have been suggested to contribute to the pathogenesis of Alzheimer's Disease and its deterioration may precede grey matter pathology. In addition, our results encourage revisiting existing neuroimaging datasets (e.g., ADNI) and clinical trials to further explore the potential of T1w/T2w to detect white matter decline or plasticity.

Our systematic review and meta-analysis summarized within-person changes in white matter diffusion tensor MRI parameters. To accurately predict the effects of clinical trials on the aging white matter, we first need to understand the direction and magnitude of naturally occurring within-person changes in older age. This study is the first review/meta-analysis synthesizing observational longitudinal changes in adult white matter microstructure, providing estimates of effect sizes, direction, and regional variability in changes in DTI parameters. By identifying individual differences in the magnitude of change in white matter microstructure, we hope to improve our ability to identify individuals at risk for dementia or in preclinical stages of the disease. This could open up new opportunities for early interventions, especially given that treatments targeting grey matter pathology have so far been ineffective in treating symptoms of cognitive impairment.

Lastly, our last manuscript showed the first application of a symmetric multimodal fusion analysis to characterize joint age differences in diffusion tensor imaging features in the white matter space. Our analyses revealed an independent component with covariate patterns of RD and AD that differentiated between young and older adults. The spatial patterns of our results were consistent with current theories of white matter vulnerability in late-myelinating regions. Joint information across RD and AD showed a superior association with processing speed and executive function than unimodal DTI analyses. These findings highlight the importance of multimodal data fusion in minimizing incorrect conclusions about age-related cognitive decline and identifying the missing links between white matter aging and cognition (Calhoun & Sui, 2016). As we continue to unlock the potential of multimodal imaging, developing better models that can complement and exploit the richness of our data will be crucial for further advancing our understanding of Alzheimer's disease and related dementias.

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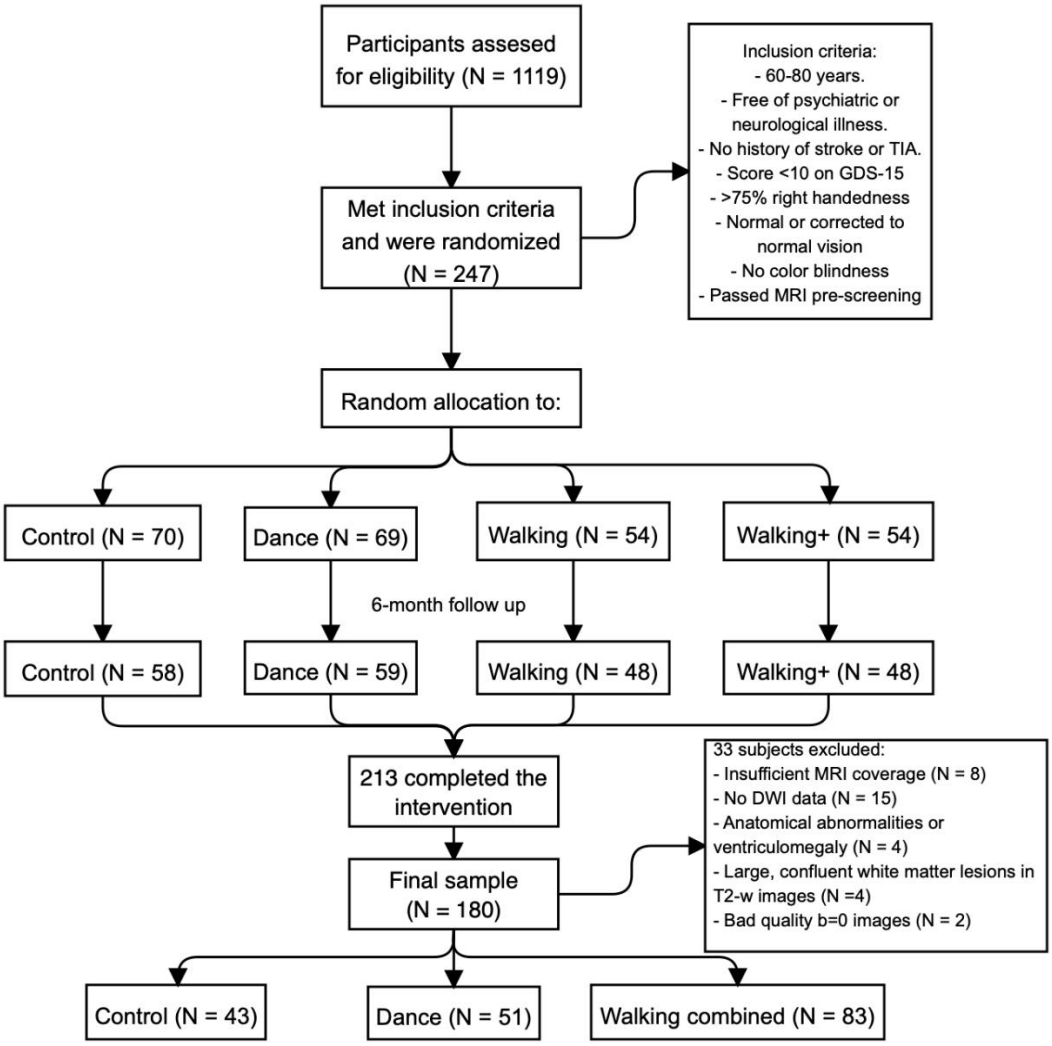

Figure. A.1.

Flowchart diagram of sample selection

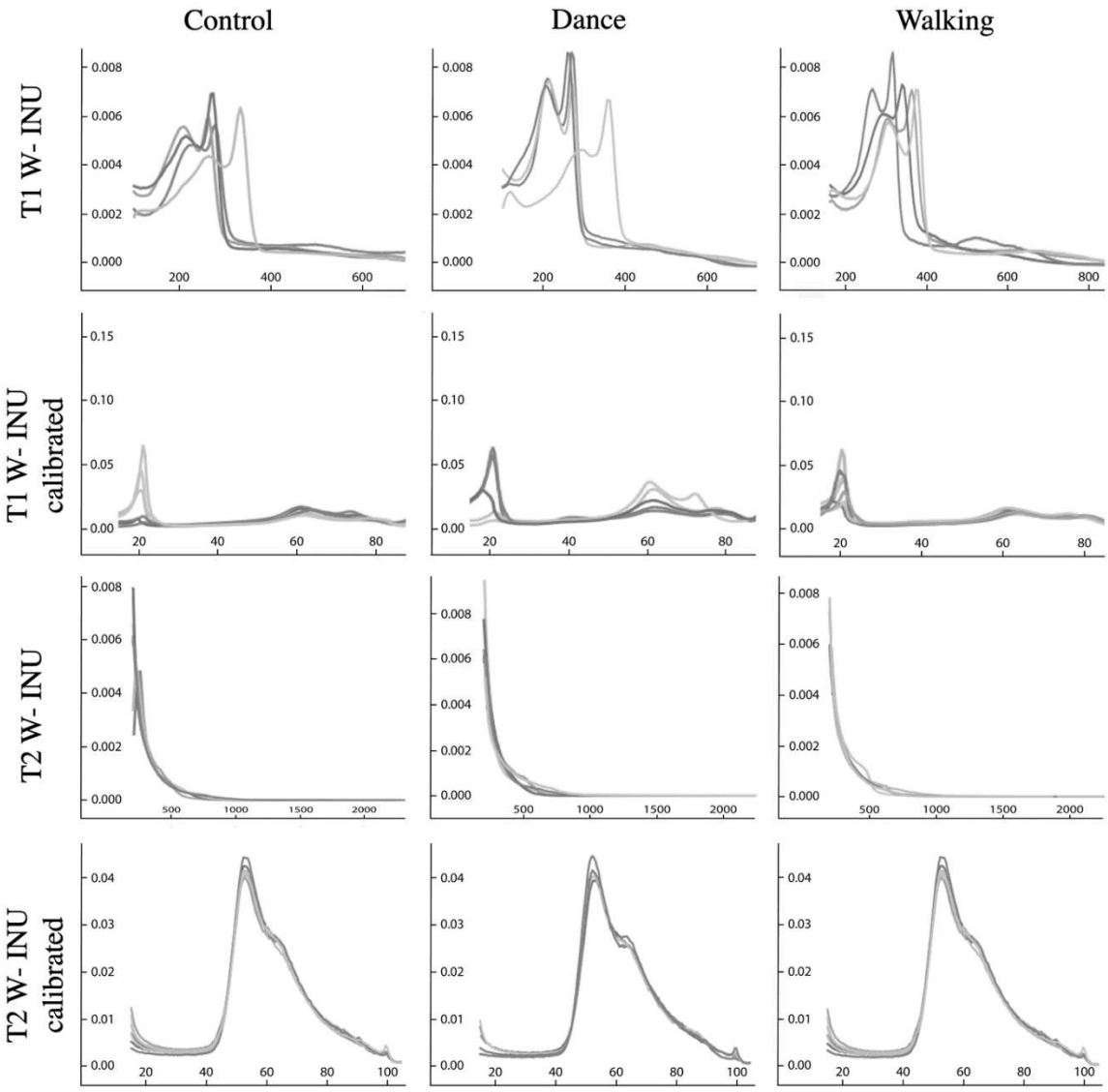

Figure. A.2.

Histograms of intensity distributions for T1w and T2w images before and after calibration for 5 random subjects from the three experimental groups. The x axis shows intensity values. The y axis shows the data series as probabilities, where the values are normalized by bin-width. INU= intensity non-uniformity. Note: Images are in native space, without skull-stripping, therefore the histograms are showing all possible intensity values, including non-brain tissues.

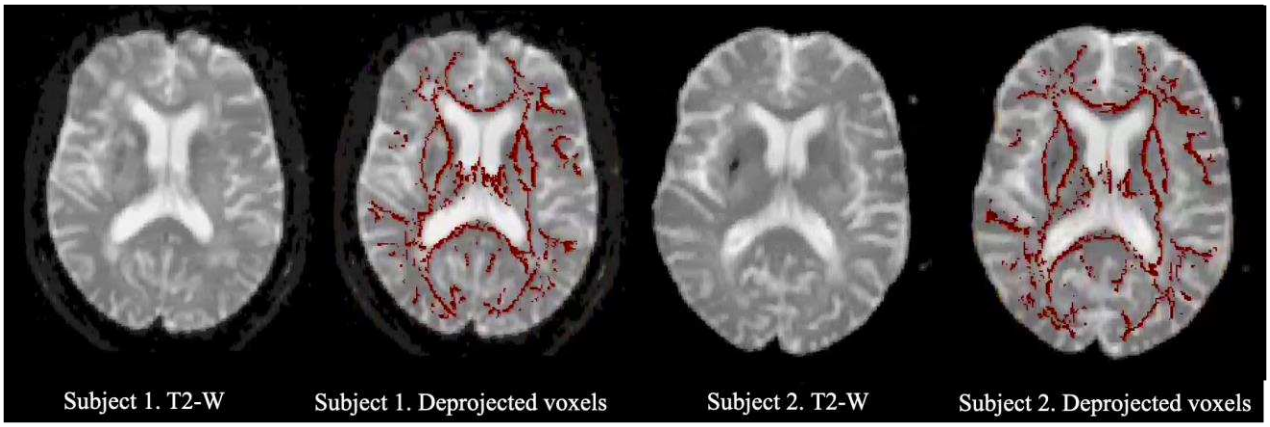

Figure A.3.
Deprojected voxels (in red) from group skeleton into native space using the FSL deproject function. Images were selected from the participants with the highest white matter lesion volumes on T1-weighted images to demonstrate the possibly most dramatic effect of white matter lesions on the skeleton projection.

Table A.1. Time-by-intervention interactions in white matter T1w/T2w

	Walking + Dance vs. Control			Walking vs. Control			Dance vs. Control		
Region	β	SE	p	β	SE	p	β	SE	p
fMAJ	0.03	0.03	0.26	0.03	0.02	0.34	0.02	0.03	0.4
CST	0.04	0.03	0.48	0.02	0.03	0.46	0.04	0.03	0.2
UNC	0.01	0.02	0.57	0.01	0.02	0.63	0.01	0.03	0.6
EC	0.02	0.03	0.49	0.02	0.03	0.53	0.02	0.03	0.6

fMAJ=forceps major; CST= corticospinal tract, UNC=uncinate fasciculus, EC=external capsule.

Table A.2. Time-by-intervention interaction coefficients to compare Dance vs. Walking interventions

	Dance vs. Walking	
Region	Standardized β	*p*
Total	0.02	0.844
CC1	-0.03	0.701
CC2	-0.01	0.996
CC3	-0.01	0.873
CC4	0.02	0.598
CC5	-0.08	0.138
Prefrontal	0.01	0.867
fMAJ	-0.01	0.722
fMIN	-0.01	0.877
Cingulum	-0.02	0.636
CST	0.02	0.485
SLF	0.02	0.728
FX	-0.02	0.550
UNC	-0.01	0.891
EC	-0.01	0.975

Table A.3. Time-by-intervention interactions in white matter T1w/T2w controlling for white matter lesion load

WM=white matter. β are standardized. Bold highlights $p<.05$.

	Walking vs. Control			Dance vs. Control		
	β	SE	p	β	SE	p
Time x WM lesion	0.09	0.12	0.43	0.09	0.12	0.43
Intervention x Time	**0.29**	0.12	0.02	**0.26**	0.14	0.05
Intervention x Time x WM lesion	-0.12	0.14	0.39	-0.14	0.14	0.33

In this model, the parameter of interest is Intervention × Time × WM lesion, which revealed no additional effect of white matter lesion load on the course of T1w/T2w over time.

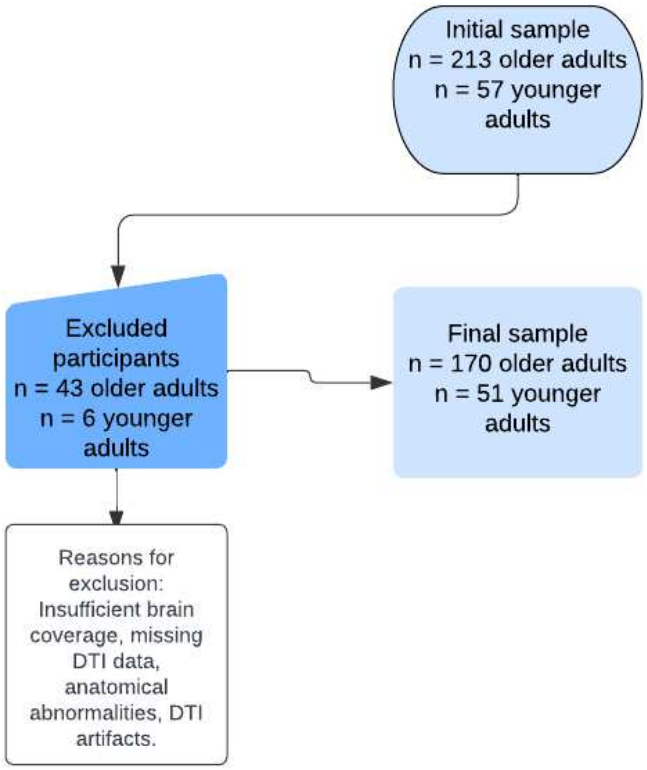

Figure A.4. *Participant flow. For the older group, out of 213 participants who completed the clinical trial, 170 had good-quality DTI and T1-weighted data. Among the 43 excluded subjects, eight had insufficient brain coverage of b=0 images for T1w/T2w calculation, n=15 had missing DTI data due to technical problems, n=8 had anatomical abnormalities or ventriculomegaly, and n=12 had artifacts in DTI data. For the young sample with female dancers, 43 had good quality DTI and T1-W data, but 6 were excluded due to insufficient brain coverage of DTI data, resulting in 37 participants being included. All 14 participants had good quality DTI and T1-W data for the young sample of college-age adults. Our final sample comprised 170 older adults (aged 60-80) and 51 younger adults (aged 18-33). insufficient brain coverage, missing DTI data, anatomical abnormalities, or DTI artifacts,*

Table A.4.

Multiple linear regression models between DTI parameters and cognitive composites

	Executive Function			Processing Speed		
	β	*p*	*q*	*β*	*p*	*q*
Model 1						
RD	0.143	0.495	0.720	-0.123	0.343	0.449
Age (years)	-2.126	0.001	0.004	-1.833	0.001	0.004
Education (years)	0.740	0.009	0.020	-0.165	0.197	0.364
Sex	0.154	0.816	0.956	-0.271	0.374	0.449
Model 2						
AD	0.056	0.890	0.956	-0.276	0.122	0.364
Age (years)	-2.161	0.001	0.004	-2.038	0.001	0.004
Education (years)	0.739	0.007	0.020	-0.158	0.214	0.364
Sex	0.211	0.751	0.956	-0.257	0.393	0.449
Model 3						
FA	0.631	0.069	0.110	-0.028	0.853	0.853
Age (years)	-1.787	0.001	0.004	-1.816	0.001	0.004
Education (years)	0.727	0.012	0.024	-0.161	0.210	0.364
Sex	0.036	0.956	0.956	-0.314	0.303	0.440
Model 4						
MD	-0.592	0.046	0.081	-0.099	0.450	0.480
Age (years)	-1.973	0.001	0.004	-1.825	0.001	0.004
Education (years)	0.723	0.008	0.020	-0.158	0.216	0.364
Sex	-0.050	0.940	0.956	-0.371	0.228	0.364

Sex is coded as 0=female, 1=male. β represents the standardized coefficients, *p* represents the uncorrected p-value, and *q* represents the false discovery rate corrected p-value. Model 1 includes RD in the whole white matter, education (years), and sex. Model 2 includes AD in the whole white matter, education (years), and sex. Model 3 includes FA in the whole white matter, education (years), and sex. Model 4 includes MD in the whole white matter, education (years), and sex.