Contributions of Prefrontal White Matter Integrity to Cognitive Performance in Healthy Aging

by

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Abstract

Aging is well-known to produce changes in the brain at both the functional and anatomical level. Increased age is associated with general brain atrophy and a decline in cognitive abilities such as executive functioning, working memory, and processing speed.

A key brain region responsible for these cognitive functions is the prefrontal cortex (PFC), which experiences disproportionately greater age-related degeneration than posterior areas of the brain. The PFC is a heterogenous structure and is often segmented into several functional subregions; it is believed these subregions may facilitate certain cognitive abilities, and damage specific to a certain subregion may result in distinct cognitive deficits in some domains while sparing others. The relationships between age, cognitive performance, and prefrontal grey matter structure have been investigated before; however, few in-vivo studies have examined how the white matter (WM) contained within these subregions is affected by aging, and whether age-related declines in WM integrity drive the declines in cognitive performance that comes with age.

Therefore, the aim of this study is to use diffusion tensor imaging (DTI) to measure age differences in the WM integrity of prefrontal subregions and determine if WM integrity is a mediator of age-related cognitive decline.

The study involved 140 participants aged 18-85 (62 men, 78 women). PFC WM was segmented into medial orbitofrontal (MOFC), lateral orbitofrontal (LOFC), medial prefrontal (MPFC), and dorsolateral prefrontal (DLPFC) components, and DTI parameters for each region were obtained. Participants were also evaluated on executive functions, working memory, processing speed, reaction times, and emotional recognition using various neuropsychological tests which were reduced to latent variables using factor analysis. To characterize the effects of age on DTI parameters more precisely, and measure their non-linear trajectories, higher order polynomial

regression modeling was utilized, while structural equation modeling was used to test for mediation effects.

We found that WM within all prefrontal subregions show age-related differences in DTI parameters, exhibiting decreases in fractional anisotropy (FA) values, increases in mean, radial, and axial diffusivities, and decreases in tract volumes and fiber counts with increased age. The majority of age effects were non-linear, best modeled using higher order powers of age in their regressions. Cognitive performance in most domains declined with increased age; however, after controlling for the effects of age, a general latent factor of PFC WM integrity was not found to mediate the age-related decline in cognitive performance. However, FA values specific to MOFC and LOFC tracts did predict performance in conceptual flexibility, visuospatial memory, reaction times, and theory of mind tasks and produced significant indirect effects of age on cognition. While FA values in the MOFC and right LOFC partially mediated age effects on cognitive ability, FA values in the left LOFC suppressed them, demonstrating the unique properties of prefrontal subregions.

The findings in this study improve our understanding of WM aging. Although the vulnerability of prefrontal WM to aging has been documented, this is the first study that measured age effects on WM integrity within prefrontal subregions and investigated whether integrity mediates age-related cognitive decline. Prefrontal subregions do not display uniform WM aging and are uniquely associated with select cognitive functions, mediating the effects of age in certain cases.

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List of Common Abbreviations

PFC: Prefrontal Cortex

WM: White Matter

GM: Grey Matter

MRI: Magnetic Resonance Imaging

DTI: Diffusion Tensor Imaging

EF: Executive Function

OFC: Orbitofrontal Cortex

MOFC: Medial Orbitofrontal Cortex

LOFC: Lateral Orbitofrontal Cortex

MPFC: Medial Prefrontal Cortex

DLPFC: Dorsolateral Prefrontal Cortex

CC: Corpus Callosum

ICV: Intracranial Volume

FA: Fractional Anisotropy

MD: Mean Diffusivity

RD: Radial Diffusivity

AD: Axial Diffusivity

ROI: Region of Interest

ICC: Intraclass Correlation Coefficient

EFA: Exploratory Factor Analysis

CFA: Confirmatory Factor Analysis

SEM: Structural Equation Modeling

CI: Confidence Interval

LO: Lower Order

HO: Higher Order

SWM: Superficial White Matter

D-KEFS: Delis-Kaplan Executive Functions System

TMT-NLS: Trail Making Test-Number Letter Switching

CWI: Color-Word Interference

CWI-I: Color-Word Interference-Inhibition

CWI-IS: Color-Word Interference- Inhibition Switch

VF: Verbal Fluency

VF-LF: Letter Fluency

VF-CF: Category Fluency

VF-CC: Category Correct

VF-CS: Category Switch

Sort-FS: Sorting Test- Free Sort

Sort-SD: Sorting Test- Sort Description

Sort-RD: Sorting Test- Recognition Description

WMS-IV: Wechsler Memory Scale 4th Edition

LM: Logical Memory Subtest

VPA: Verbal-Paired Associates

DE: Designs Subtest

SA: Spatial Addition

SSP: Symbol Span

SRT: Simple Reaction Time

CRT: Choice Reaction Time

PASAT: Paced Auditory Serial Additions Test

RMET: Reading the Mind in the Eyes Test

PET: Positron Emission Tomography

fMRI: Functional Magnetic Resonance Imaging

WMH: White Matter Hyperintensities

1. Introduction

1.1 Aging and Prefrontal Functions

Healthy cognitive aging is the term used to describe the expected trajectory of brain aging free of neurodegenerative diseases and conditions that produce substantial cognitive impairment. However, even in the absence of neuropathology, advanced age in otherwise healthy individuals has been associated with a decline in various cognitive functions, including memory, planning, processing speed, and attention (Salthouse, 2010; Harada *et al.*, 2013). The greatest losses tend to occur in processes reliant on speed and fluid intelligence, while crystallized intelligence is often preserved (Craik & Salthouse, 2011). Healthy cognitive aging also imposes changes on neuroanatomical structure; in-vivo magnetic resonance imaging (MRI) studies have found reductions in both grey (GM) and white (WM) matter volumes (Gunning-Dixon *et al.*, 2009; Lockhart & DeCarli, 2014), thinning of cortex (Raz & Rodrigue, 2006; Fjell *et al.*, 2014), and reductions in WM integrity (Cox *et al.*, 2016) to be hallmarks of typical brain aging. However, the rate of atrophy is not uniform across the brain. Compared to posterior areas, the frontal lobes suffer disproportionately greater signs of decline with advancing age (Allen *et al.*, 2005; MacDonald & Pike, 2021); the prefrontal cortex (PFC), the anterior-most region of the frontal lobes, is especially vulnerable to the effects of age (Fjell & Walhovd, 2010; Cabeza & Dennis, 2012). The greater susceptibility of the PFC to age led to the development of the "Frontal Theory of Aging" (Raz, 2000) which suggests that age-related cognitive decline is mediated by the preferential deterioration of the PFC.

The PFC is responsible for numerous complex processes such as emotional regulation, working memory, and executive functioning (Cabeza & Dennis, 2012; Fuster, 2015; Zanto & Gazzaley, 2019); therefore, age-related atrophy of the PFC may result in deficits in these domains. Executive functions (EF), defined as a family of top-down mental processes involved in making effortful and purposeful behaviour (Diamond, 2013; Friedman & Miyake, 2017), are dependent on the PFC. PFC atrophy, including age-related degeneration, has been shown to impair performance on EF tasks involving cognitive flexibility, attention shifting, and inhibition of responses (Alvarez & Emory, 2006; Yuan & Raz, 2014). Working memory describes the temporary storage of task-relevant information in an easily accessible form that allows for its inspection and manipulation; it involves holding stimuli that are no longer present, disassembling them, and incorporating new

information or applying rules to help drive goal-directed behavior (Braver & West, 2008; Diamond, 2013).

While working memory is often regarded as a component of EF it can be studied separately, as working memory is associated more with storage capacity and focused attention than set shifting and decision making (Baddeley, 2003; D'Esposito, 2008; Oberauer, 2019). Unlike EFs, which are believed to be spread across the PFC due to their complexity (Stuss & Alexander, 2000; Fuster, 2001; Alvarez & Emory, 2006), working memory appears localized to the dorsolateral portion of the PFC (Manes *et al.*, 2002; Blumenfeld & Ranganath, 2006; Barbey *et al.*, 2013; Szczepanski & Knight, 2014), demonstrating a functional heterogeneity of certain PFC regions. Localized functional specificity is not limited to working memory; other functions performed by the PFC, such as emotional recognition, social behaviour, and reinforcement learning are linked predominantly with the inferior-most orbital PFC (Rolls, 2004; Cummings & Miller, 2007; Zald & Andreotti, 2010). The medial PFC, in contrast, has been associated with both orbital and dorsolateral PFC processes (Carrington & Bailey, 2009; Tsuchida & Fellows, 2009; Hiser & Koenigs, 2018) and more general PFC functions, such as prospective planning and decision making (Manes *et al.*, 2002; Chib *et al.*, 2009).

This observed neurocognitive specialization within the PFC prompted the development of measurement tools sensitive to these functional subdivisions. MRI studies in particular developed protocols to segment the PFC into distinct subregions and analyze them separately, as it was likely that abnormalities or atrophy in distinct subregions would be preferentially associated with losses in particular PFC functions (Yuan & Raz, 2014).

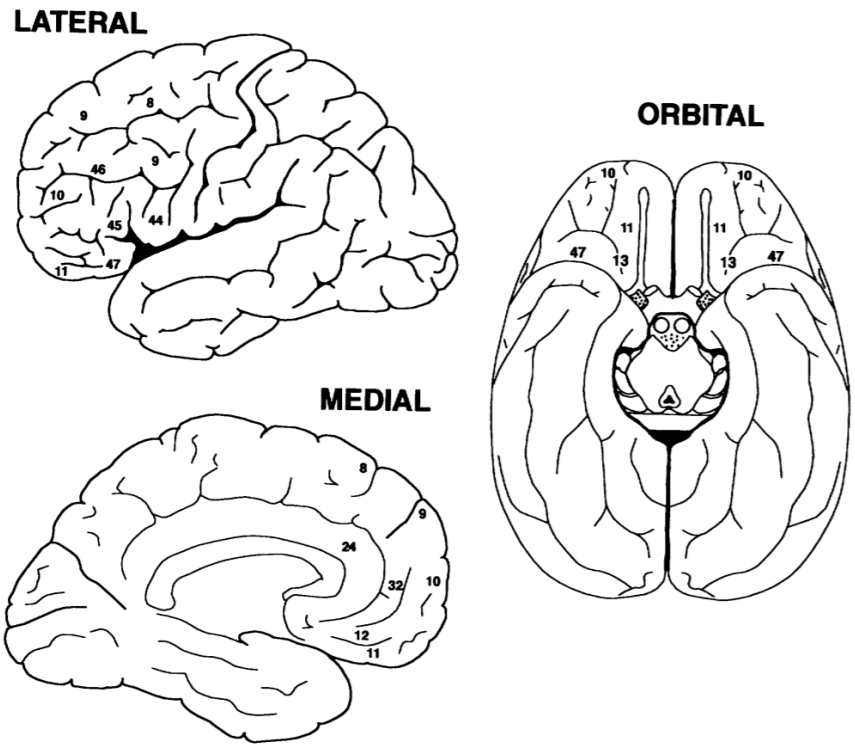

Figure 1. Parcellation of the frontal lobe into 3 components: lateral, medial, and orbital. Numbers correspond to Brodmann areas. Illustration obtained from Fuster (2002).

1.2. Prefrontal Subregions

The prefrontal cortex is a complex and heterogenous structure that can be divided into distinct anatomic or functional subregions. The earliest classifications of PFC subdivisions were based on regional cytoarchitectonic characteristics. Various histological staining methods (Ongur *et al.*, 2003) were used to distinguish regions based on cellular architecture, cortical cell types, cortical lamina thickness, and even subcortical circuitry (Barbas & Pandya, 1989; Pandya & Yeterian, 1996; Tekin & Cummings, 2002). However, due to differences in methodology and disagreement on overlapping primate comparisons, unanimous agreement regarding which cytoarchitectonic areas comprise certain PFC subregions has not been reached (for review see Petrides *et al.*, 2012).

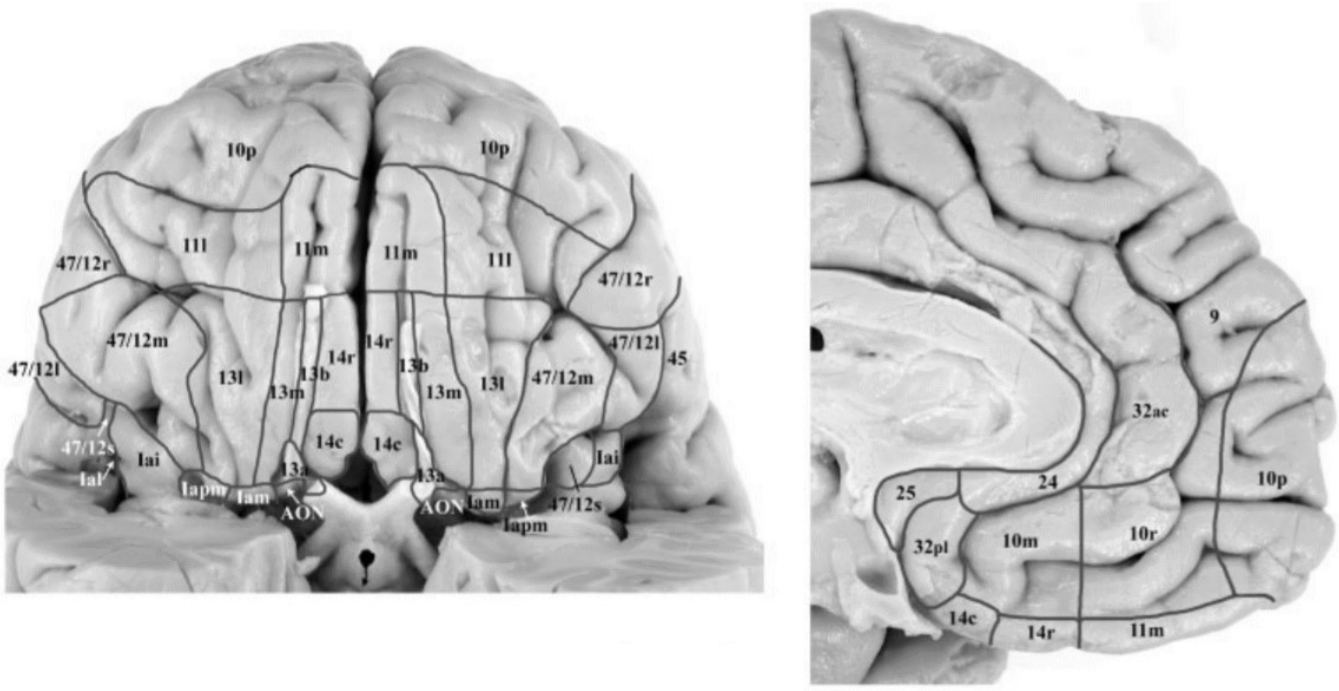

Figure 2. Cytoarchitectonic subdivisions of the human prefrontal cortex. Subdivisions are shown on a coronal (left) and midsagittal view (right) as delineated by Ongur *et al.* (2003).

Broadly, the PFC is generally subdivided into a lateral, medial, and orbital component (Figure 1), with the orbital section frequently subdivided further into lateral and medial parts (see Zald *et al.*, 2014). These general subdivisions, unlike the gyrus-level specific architectonic delineations, can be distinguished and visualized using MRI. Previous MRI studies (Howard *et al.*, 2003) have parcellated the PFC into dorsolateral prefrontal (DLPFC), medial prefrontal (MPFC), medial orbitofrontal (MOFC), and lateral orbitofrontal (LOFC) subregions (Figure 3) with subsequent studies improving the method to be more specific to function localization rather than using anatomical landmarks (Ranta *et al.*, 2009). MRI studies investigating the effects of aging on PFC subregions found varying results, showing greater declines in MPFC and DLPFC GM volumes compared to the orbitofrontal (OFC) subregions (Zimmerman *et al.*, 2006; Cowell *et al.*, 2007), while other studies report similar age effects across regions (Raz *et al.*, 1997; Raz *et al.*, 2004).

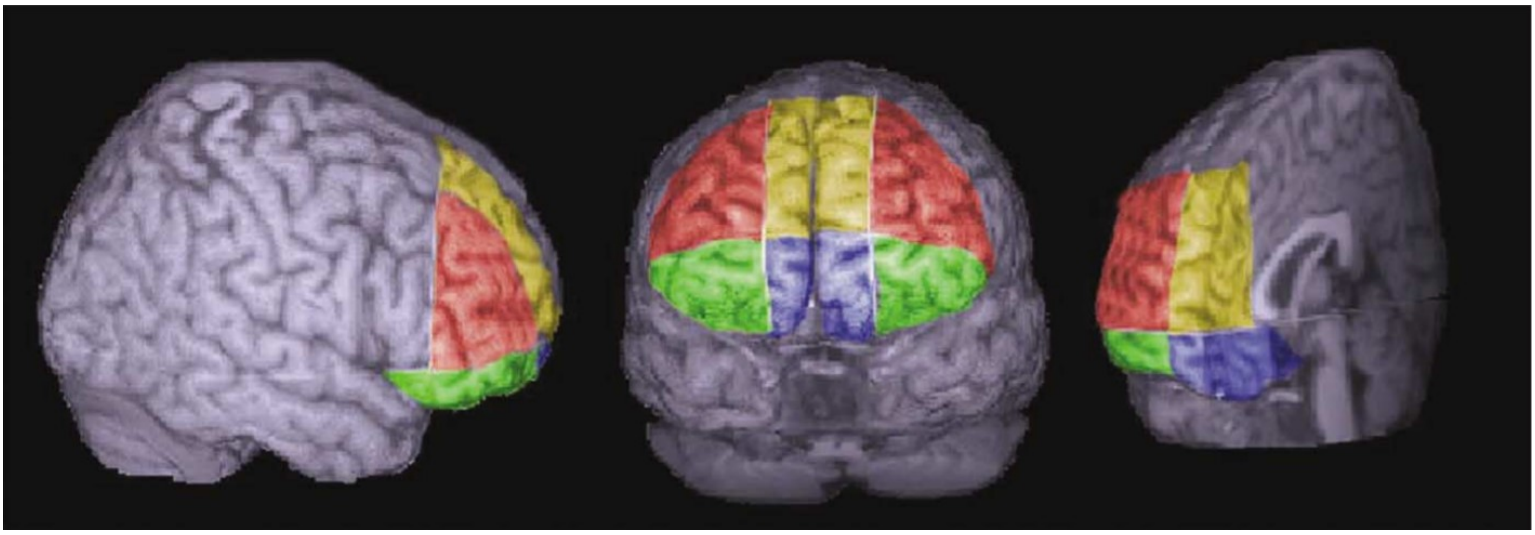

Figure 3. Parcellations of the prefrontal cortex (PFC) in MRI. The PFC is segmented into dorsolateral (red), medial prefrontal (yellow), lateral orbitofrontal (green), and medial orbitofrontal (blue) subregions. Figure obtained from Howard *et al.* (2003).

These differential effects of aging on PFC anatomy may explain the vulnerability of certain types of cognitive processes to aging while others are spared, namely greater effects of age on DLPFC and MPFC mediated functions (West, 1996; Phillips & Della Sala, 1998; MacPherson *et al.*, 2002). Compared to PFC GM, studies investigating the effects of aging on the WM contained within PFC subregions are less common (Salat *et al.*, 2005; Malykhin *et al.*, 2011) and suggest WM exhibits a reversed vulnerability of age, with ventromedial WM volumes experiencing greater age-related atrophy than lateral WM. Medial prefrontal WM was also further divided into interhemispheric WM passing through the corpus callosum (CC) and non-callosal portions (Figure 4), with greater age-effects occurring in callosal WM. As myelin forms a significant component of WM, age-related differences in WM loss across subregions may be due to their varying myelin content (Ongur *et al.*, 2003) since the onset and extent of myelination that occurs during development is not uniform across the PFC (Kinney *et al.*, 1988; Tamnes *et al.*, 2010; Nieuwenhuys & Broere, 2017). With the aid of MRI techniques specialized for visualizing WM, such as diffusion tensor imaging (DTI), measures more sensitive to WM aspects such as axonal integrity or degree of myelination can be obtained. Such tools can more effectively isolate the WM within prefrontal subregions and measure their unique relationships with age.

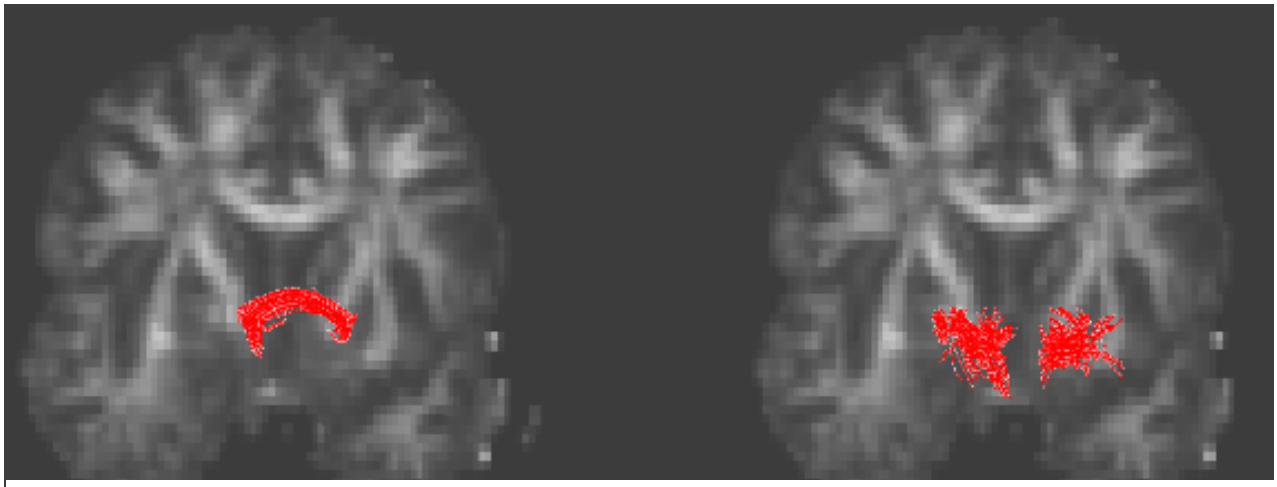

Figure 4. Separation of MOFC white matter into callosal (left) and non-callosal (right) components. The same extraction is also performed on the medial prefrontal white matter.

1.3. Diffusion Tensor Imaging

Volumetric WM imaging, much like GM imaging, provides gross macroscopic metrics less sensitive to aging effects which also occur on a microstructural level (Fjell *et al.*, 2008; Hugenschmidt *et al.*, 2008). Diffusion tensor imaging (DTI) is an MRI technique that enables the measurement of WM microstructural properties in vivo (Assaf & Pasternak, 2008) and extraction of parameters strongly associated with aging (Burgmans *et al.*, 2010; Giorgio *et al.*, 2010). DTI quantifies the directionality of intravoxel water diffusion, with hindered water diffusion attributed to obstructions from axons, cell bodies, and myelin (Pierpaoli & Basser, 1996; Beaulieu, 2002; Sen & Basser, 2005).

The primary DTI parameter used to describe intravoxel water diffusion is fractional anisotropy (FA), ranging from 0 (fully isotropic diffusion) to 1 (fully anisotropic diffusion), FA describes the shape of the diffusion ellipsoid within a voxel and functions as an indirect measure of WM integrity. High FA values indicate high fiber coherence and dense axonal packing as water diffusion predominantly occurs parallel to fiber tracts with limited perpendicular diffusion, while low FA values are usually due to higher diffusion perpendicular to tract orientation (Beaulieu, 2014). Decreases in FA, known to occur with aging (Burzynska *et al.*, 2010; Molloy *et al.*, 2021), may therefore correspond to a wide range of microstructural processes, including fiber

reorganization, axonal degeneration, and demyelination. The magnitude of intravoxel water diffusion can also be separated solely into components parallel to, and perpendicular to, the preferential diffusion direction measured by FA, termed axial (AD) and radial (RD) diffusivity respectively. In addition, a mean diffusivity (MD), averaging the magnitude of diffusivity in all directions within a voxel can be calculated.

Changes in these DTI parameters may reflect unique microstructural phenomena, with AD associated with axonal degeneration (Sun *et al.*, 2008; van de Looij *et al.*, 2012) and RD with demyelination (Song *et al.*, 2002; Song *et al.*, 2005); therefore, DTI analysis that includes all diffusion characteristics provides a more comprehensive examination of WM integrity

Since voxel FA values contain directionality believed to represent the direction of propagating fiber bundles, DTI can also be used to perform tractography wherein adjacent voxels with similar directionality are connected to visualize the structure of entire WM tracts (Basser *et al.*, 2000; Mori & Zhang, 2006). This allows for DTI to extend beyond voxel level analysis and instead measure properties of fiber bundles that comprise specific WM tracts within the brain; by averaging the FA values of all voxels making up the tract, an estimate of whole tract integrity can be derived. Furthermore, DTI-tractography enables analysis of tract macrostructural properties. By obtaining the number of voxels covered by the tract, tract volumes, fiber counts, and average fiber lengths can be calculated.

DTI has been used to examine the effects of aging on numerous WM tracts, including the cingulum bundle (Sala *et al.*, 2012; Sibilia *et al.*, 2017; Aghamohammadi-Sereshki *et al.*, 2021), uncinate fasciculus (Hasan *et al.*, 2009a; Bennett *et al.*, 2015; Aghamohammadi-Sereshki *et al.*, 2021), fornix (Malykhin *et al.*, 2008; Michielse *et al.*, 2010; Sala *et al.*, 2012), superior longitudinal fasciculus (Perry *et al.*, 2009; Lebel *et al.*, 2012; Storsve *et al.*, 2016), inferior longitudinal fasciculus (Lebel *et al.*, 2012; Sasson *et al.*, 2013; Storsve *et al.*, 2016), occipitofrontal fasciculus (Perry *et al.*, 2009; Martensson *et al.*, 2018), and the corpus callosum (Hasan *et al.*, 2009b; Lebel *et al.*, 2010; Sullivan *et al.*, 2010a; Pietrasik *et al.*, 2020). These studies, among others (Sullivan *et al.*, 2006; Davis *et al.*, 2009; Brickman *et al.*, 2012), have consistently observed the presence of an anterior-posterior gradient in age-related changes in DTI parameters, with greater decline in FA and increase in diffusivity in the anterior regions of the brain. This gradient extends to the frontal lobes as WM within the anterior PFC appears to be the most affected by aging (Burgmans *et al.*,

2010; Bartzokis *et al.*, 2012). The greater susceptibility of frontal WM is believed to occur due to its late myelination during development, leading to a "last-in-first-out" component of the Frontal Theory of Aging. Late myelinating frontal areas receive less myelin compared to posterior regions and have narrower axon fibers (Bartzokis, 2004); such fibers are known to atrophy the most during aging (Marner *et al.*, 2003).

In addition to the anterior-posterior effect, most DTI aging studies found that the decreases in FA and increases in diffusivity characteristic of aging do not follow a linear trajectory (Hasan *et al.*, 2007; Westlye *et al.*, 2010; Inano *et al.*, 2011). Instead of following a linear relationship with age, measures of WM integrity remain relatively stable during young adulthood and often do not decline until middle age. These declines at later ages are also often marked by precipitous, exponential, increases or decreases with accelerating age effects occurring in the elderly. While this prompted the adoption of non-linear modeling to characterize age-related effects (Hsu *et al.*, 2010; Michielse *et al.*, 2010; Malykhin *et al.*, 2011), using lower order (quadratic and cubic) polynomial regression continues to impose shape restrictions on the data (Fjell *et al.*, 2010), limiting proper visualization of the aging trajectory. The use of higher order polynomial regression (Malykhin *et al.*, 2017; Pietrasik *et al.*, 2020) may be required to properly describe the trajectory of WM aging.

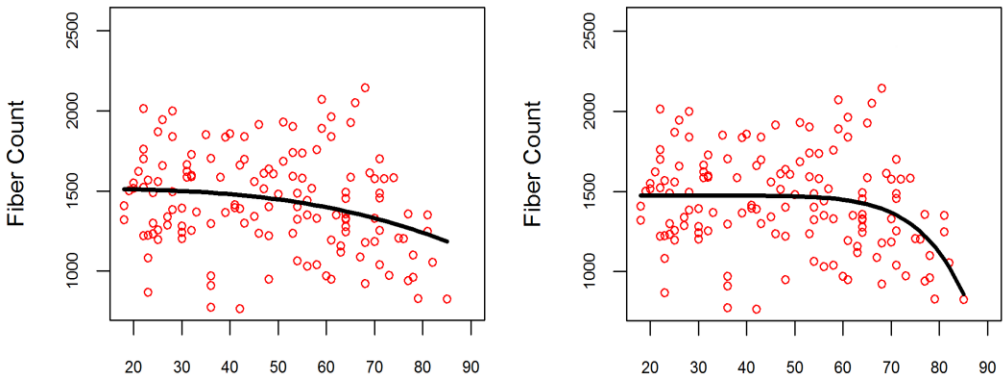

Figure 5. Comparison between lower order (left) and higher order (right) polynomial regression. Age effects on fiber count values of the splenium of the corpus callosum were modeled using a lower order cubic power of age and a higher order decic power. Lower order models impose greater shape restrictions on the data and do not properly visualize the true trajectory of fiber count decline. Higher order models provide a more accurate model, with pronounced declines occurring at 60 years of age after midlife stability. Figure obtained from Pietrasik *et al.* (2020).

1.4. DTI and Cognition

As both WM integrity and cognitive performance are known to decline with age, various studies have attempted to link age-related differences in DTI parameters to reduced cognitive performance (Bennett & Madden, 2014). Greater WM integrity, as measured by DTI parameters, is typically associated with better cognitive performance, and this relationship often persists after controlling for age. Indiscriminate of the tracts analyzed, numerous DTI studies have found links between WM microstructure and executive functions (Ryan *et al.*, 2011; Haasz *et al.*, 2013; Sasson *et al.*, 2013; Ohtani *et al.*, 2017), processing speed and reaction time (Schiavone *et al.*, 2009; Gold *et al.*, 2010; Borghesani *et al.*, 2013), and working or episodic memory (Kennedy & Raz, 2009; Bendlin *et al.*, 2010; Strenziok *et al.*, 2013). In addition to cognitive measures specific to certain domains, DTI parameters have also been associated with composite metrics of general intelligence (Cremers *et al.*, 2016; Ohtani *et al.*, 2017). Depending on a priori hypotheses, studies may opt to investigate specific tracts believed to contribute to a cognitive task or perform broad full-brain analyses. Although many correlations between DTI parameters and cognitive scores remain significant after controlling for age, the effect sizes are greatly attenuated, suggesting that a large portion of the FA-cognition relationship is driven by age (Madden *et al.*, 2012).

To determine whether WM integrity has a direct effect on cognitive performance, or whether age-related cognitive decline is caused by changes in WM integrity, mediation analysis is required (see Salthouse, 2011). Mediation analysis can be used to separate the cognitive performance variance associated with age into two components, one driven by WM integrity, and one independent of WM integrity. WM integrity, as measured by DTI parameters, is identified as a significant mediator if it retains a significant direct effect with cognitive scores after controlling for age, and if age-related variance in cognitive performance is attenuated when WM integrity is included in the regression model predicting cognitive performance (Cheung & Lau, 2008; Bennett & Madden, 2014). Several DTI studies have investigated whether FA values mediate the relationship between age and processing speed (Kerchner *et al.*, 2012; Salami *et al.*, 2012; Kuznetsova *et al.*, 2016), reaction times (Bucur *et al.*, 2008; Madden *et al.*, 2009), and various fluid intelligence measures (Perry *et al.*, 2009; Kievit *et al.*, 2014; Gazes *et al.*, 2016; Fan *et al.*, 2018). However, these studies are limited in performing simple univariate mediation that does not account for additional covariates and potentially prone to measurement errors.

The application of structural equation modeling (SEM) aims to resolve these concerns; SEM can perform multivariate mediation analyses and control for covariance between predictor variables. SEM techniques can also perform dimensionality reduction and extract common variance within similar cognitive tests and reduce them to latent factors, thus controlling for measurement error and test specific variance (Burgmans *et al.*, 2011; Bagozzi & Yi, 2012). Despite these statistical advantages, few studies have utilized SEM to investigate potential effects of WM integrity on age-related cognitive decline, and results have been largely inconsistent due to varying model structure and improper pathway analysis that did not test for true indirect effects. Instead of measuring DTI parameters of specific tracts, several studies (Charlton *et al.*, 2008; Burgmans *et al.*, 2011; Yang *et al.*, 2015) investigated integrities in broad WM regions and their mediating effect on cognitive performance. Neither study found a mediating effect of FA, MD, or RD values on processing speed, executive functions, or working memory, with limited significant mediations found in AD values for processing speed. Voineskos *et al.* used SEM to investigate the effects of callosal and long association tract FA values on cognitive performance and found several significant direct effects of FA on verbal fluency, working memory, and EF tasks; however, independent pathways between age and cognition were not drawn and mediation was not tested (Voineskos *et al.*, 2012). Apart from one study that analyzed a general prefrontal WM region and found no mediating effects of prefrontal FA on working memory, reaction time, or episodic memory tasks (Head *et al.*, 2008), previous research has largely ignored WM within the PFC despite the region's association with cognitive ability. One study (Nazeri *et al.*, 2015) examined the mediating role of superficial white matter (SWM) FA, including SWM within the PFC, on processing speed and visuomotor attention. Although SWM FA within precentral gyri, corresponding to the DLPFC, mediated processing speed, these effects were not PFC specific as SWM within the right occipital lobe was also a significant mediator.

No study has performed a manual segmentation of PFC subregions using DTI-tractography and examined how these subregions may be related to cognitive performance using SEM mediation analysis. In addition to examining mediation of the effects of age, there is a dearth of studies that utilize the multivariate capabilities of SEM to consider additional variables that may affect cognition and WM microstructure, such as sex, total intracranial volume, and years of education.

1.5. Objective

Prefrontal WM is disproportionately susceptible to the effects of aging, with greater age-related declines in WM integrity and volume compared to posterior WM. In addition, cognitive abilities dependent on PFC structure, such as executive functions, working memory, and processing speed, are among the most affected by aging. The PFC can be segmented into distinct functional subregions; a preferential decline in WM integrity of specific subregions may explain the vulnerability or sparing of certain cognitive functions with age. However, there is a lack of studies examining the differences in prefrontal WM integrity due to age and whether age-related differences in prefrontal WM have a mediating effect on the age-related decline in cognitive ability.

Therefore, the goals of this study are twofold:

1. Using deterministic DTI-tractography, age differences in WM microstructure and macrostructure of prefrontal subregions will be evaluated in a sample of 140 healthy adults, aged 18-85. PFC WM will be manually segmented into medial orbitofrontal (MOFC), lateral orbitofrontal (LOFC), medial prefrontal (MPFC), and dorsolateral prefrontal (DLPFC) subregions using a reliable protocol (Malykhin *et al.*, 2011). The effects of age on various DTI parameters, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), fiber count, average fiber length, tract volume, and average fibers per voxel will be analyzed.

   As age effects tend to be non-linear, higher order polynomial regression modelling will be used to characterize their trajectories, as done previously (Pietrasik *et al.*, 2020).These multiple regression models may include numerous powers of age, as well as other predictors, such as ICV, sex, and interaction terms, as potential predictors. These models allow us to visualize effects and trends that would otherwise be missed with lower order non-linear or linear modeling.

2. Whether the effects of age on WM integrity mediate the relationship between age and cognitive performance will be investigated using a structural equation modeling (SEM) framework. Cognitive performance will be assessed using various neuropsychological tests

examining executive functions, memory, processing speed, reaction time, and theory of mind. SEM utilizes a multivariate approach that will account for covariance between predictive variables, providing a more accurate calculation of the effects age and other variables have on cognitive ability. SEM allows for the testing of statistical mediation, or the presence of a significant indirect effect, to determine if age effects on cognitive performance are partially driven by WM integrity.

In accordance with our previous study (Malykhin *et al.*, 2011), we predict that all subregions will show an age-related decline in WM integrity manifesting as decreases in FA, tract volumes, and fiber counts, and increases in diffusivity parameters. Relationships with age are expected to be predominantly non-linear, with higher order models providing best fit in most cases. Increased age will likely be associated with reduced performance on most cognitive tasks.

Although prefrontal subregions may differ in anatomy and function rendering certain regions more susceptible to age effects and associated more with specific cognitive tasks, we have no a priori hypothesis regarding which region's WM integrity should display significant mediative effects. Despite functional specificity, damage to any PFC subregion has been found to carry broad deficits of PFC functions and differences found in histological studies are difficult to relate to subregions as defined using DTI; this study is therefore exploratory in nature. Nonetheless, this study will greatly contribute to knowledge in the field. Although associations between aging and WM integrity, the PFC and cognitive performance, and WM and cognitive performance, have been well documented, this is the first study to examine whether the effects of age on the WM within prefrontal subregions affects cognitive performance. Thus, this study will provide us with insight regarding the role of prefrontal WM in healthy cognitive aging.

2. Methods

2.1. Participants

Participants were recruited using online, poster, and local advertisements; over 300 candidates were screened to determine eligibility for the study of which 152 met the inclusion and exclusion criteria and completed the MRI procedure. Twelve subjects were removed from final analysis due to the detection of substantial movement in either structural MRI or DTI datasets during quality control. The final study sample (Table 1) consisted of 140 individuals (62 men, 78 women), ages 18-85, (mean 48.3 years, SD= 18.4), with 46 participants over the age of 60. The majority of participants were university educated individuals, 106 were Caucasian (75.7%), 26 Asian (18.6%), 7 Latin American (5%), and 1 African (0.7%); additionally, most were right-handed (R: 123; L: 16), as determined by laterality quotients ≥ +80 on the Edinburgh Handedness Inventory (Oldfield, 1971).

	Number	**Age in years (mean ± SD)**	**Education in years (mean ± SD)**	**Handedness (R/L)**	**ICV in cm^3 (mean ± SD)**
Male	62	48.31 ± 19.51	16.19 ± 2.44	56/6	1739.75 ± 137.02
Female	78	48.24 ± 17.72	15.47 ± 2.44	68/10	1510.20 ± 112.73
Total	140	44.69 ± 18.42	15.79 ± 2.46	124/16	1611.86 ± 168.45
Test Statistic	-	F=0.03	F=1.17	Z=0.699	F=10.88
p value	-	0.98	0.085	0.48	<0.001

Table 1. Participant Information. ICV: intracranial volume

Candidate screening involved a phone interview for existing neuropsychiatric disorders and MRI contraindications. Individuals with medical illness that may interfere with cognitive function (neurodegenerative diseases, cerebrovascular pathology, tumors or congenital malformations, epilepsy, dementia, stroke), or history of psychiatric or neurological disorders, including those in first-degree relatives, as assessed by the Anxiety Disorders Interview Schedule-IV (Brown *et al.*, 2001) were excluded from the study. Candidates were also excluded if they disclosed a history of current or past use of psychotropic medications and recreational drugs. Face-to-face interviews were conducted to verify healthy cognitive function in older individuals. Older subjects (>50 years) displaying mild cognitive impairment (MCI) or dementia were excluded from the study. Dementia was defined according to DSM-IV criteria; MCI was defined by the presence of cognitive complaints as documented on the AD-8 (Galvin *et al.*, 2007) with documented

impairment (score < 26) on the Montreal Cognitive Assessment Test (MOCA; Nasreddine *et al.*, 2005). Participants over 50 were also assessed for vascular dementia with the Hachinski Ischemia Scale (Hachinski *et al.*, 1975); considering that Hachinski scores above 7 out of 18 have an 89% sensitivity (Moroney *et al.*, 1997) for vascular dementia, all participants included in this study had scores of 3 or lower.

In elderly candidates, the Clinical Dementia Rating Scale (CDR) was used as an additional screening measure for dementia. CDR was used to rate dementia symptom severity (Hughes *et al.*, 1982); subjects were assessed for performance in memory, orientation, judgement & problem solving, community affairs, home and hobbies, and personal care; a composite score between 0 and 3 was then calculated. All participants in the study met the cut-off total CDR score of 0.5. Elderly subjects were also excluded if they showed depressive symptoms. To screen for depression in the elderly the Geriatric Depression Scale (GDS) was utilized (Yesavage *et al.*, 1982), in which a score of >5 is suggestive of depression and a score of >10 is indicative of depression; all elderly subjects in this study met the cutoff score of ≤4. Written informed consent was obtained from participants, and the research was approved by the University of Alberta Health Research Ethics Board.

2.2. MRI Acquisition

Participants were scanned on a Siemens Sonata 1.5T scanner (Erlangen, Germany). A cradle and bilateral head supports were used to reduce subject motion. A high resolution T1-weighted 3D magnetization prepared rapid gradient echo (3D MPRAGE) sequence of the whole brain [TR: 2080 ms; TE: 4.38ms; TI: 1100ms; flip angle: 15°; bandwidth: 130Hz/Px; FOV: 256×192×144 mm^3 ; voxel size: $1mm^3$ isotropic, scan time 5min 49sec] oriented perpendicular to the anterior-posterior commissure line (AC-PC line) and parallel to the midline was obtained for estimation of intracranial volume (Eritaia *et al.*, 2000). DISPLAY (Montreal 7 Neurological Institute, QC, Canada) software was used to trace the ICV. Diffusion data sets for DTI were acquired using a twice-refocused spin echo, echo planar imaging sequence (Reese et al., 2003) with the following parameters: TR=7700 ms, TE=94ms, 5 non-diffusion weighted volumes (b=0 s/mm^2), 30 diffusion

directions (b=1,000s/mm^2), 50 slices, FOV: 212×212×111mm^3, voxel size: 2.2x2.2x2.2mm isotropic, with full brain coverage without gap, and a scan time of 4 min 39sec.

2.3. MRI Data Analysis & Tractography Protocol

Diffusion data sets were transferred to a personal computer running DTIStudio v2.40 (Johns Hopkins University, Baltimore, MD), which uses the Fiber Assignment by Continuous Tracking (FACT) algorithm for DTI tractography (Mori *et al.*, 1999; Jiang *et al.*, 2006). Tracts were acquired by seeding each voxel with a FA value greater than 0.2 until they reached a voxel with an FA less than 0.2, or an angular deviation of >60° from the propagating line. To correct for subject motion and eddy current distortion, DTI data sets were pre-processed by rigid body co-registration to the b0 image using Automatic Image Registration (AIR) in DTIStudio. Tracts were delineated when they penetrated 2D Regions of interest (ROI) based on anatomical landmarks that were drawn on the principal direction color maps which illustrate the main orientation of diffusion within each voxel. Tract-specific fractional anisotropy, eigenvectors (λ_1, λ_2, λ_3) to calculate axial (λ_1), radial $\left(\frac{\lambda_2+\lambda_3}{2}\right)$ and mean $\left(\frac{\lambda_1+\lambda_2+\lambda_3}{3}\right)$diffusivity, tract fiber count, average tract length, average number of fibers per voxel, and tract voxel count were all calculated within DTIStudio and obtained. Tract volume was the product of voxel count and interpolated voxel size, 2.2mm^3. Volumes of specific white matter tracts were adjusted for individual ICV, according to the formula: ICV-adjusted volume = Raw tract volume (mm^3) / ICV of the same individual (cm^3) × sample average ICV (cm^3) (Malykhin *et al.*, 2017).

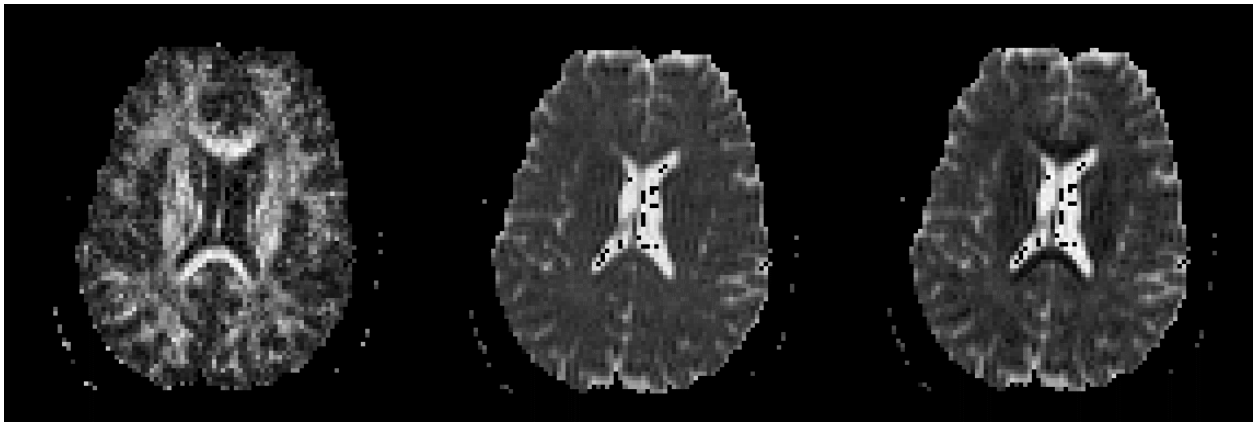

Figure 6. FA (left), tensor trace (sum of three eigenvalues; middle), and RD (right) maps.

The tractography protocol, which segmented the prefrontal cortex into orbitofrontal, medial prefrontal, and dorsolateral prefrontal white matter subregions (Figure 6) was adapted from our previous study (Malykhin *et al.*, 2011). The orbitofrontal white matter was defined as the white matter connections below the lowest border of the genu of the corpus callosum as seen on an axial slice. Orbitofrontal WM was further divided into medial (MOFC) and lateral (LOFC) subsections based on the lateral boundary of the medial WM which nominally lies along the medial orbital sulcus. The posterior borders of the MOFC extended to the posterior-most border of the genu, while in the LOFC the ROI included all WM anterior to the temporal lobe as seen in the axial slice. "NOT" ROIs were placed 2 slices posterior to these posterior borders to remove posteriorly-projecting association fibers, not ROIs placed 2 slices medial or lateral to the MOFC-LOFC division were placed to remove spurious medial or laterally projecting fibers for the LOFC and MOFC, respectively. Another "NOT" ROI was placed 2 slices superior to the superior-most ROI to remove superiorly projecting non-callosal WM from the MOFC; the MOFC was separated into callosal and non-callosal segments using a midsagittal "AND" ROI.

WM above the closure of the genu as seen in axial slices was divided into medial (MPFC) and dorsolateral (DLPFC) prefrontal WM, with a medial-lateral delineation defined in axial slices in a similar way to the OFC tracts. WM projecting from the genu formed the lateral boundary of the medial prefrontal WM, lateral WM past this boundary belonged to the DLPFC. "NOT" ROIs were applied 2 slices posterior to the posterior boundaries to remove posteriorly projecting fibers for both the MPFC and DLPFC, alongside a "NOT" ROI 2 slices inferior to the inferior border to remove fibers belonging to the OFC. The MPFC was also segmented into callosal and non-callosal WM with a midsagittal "AND" ROI.

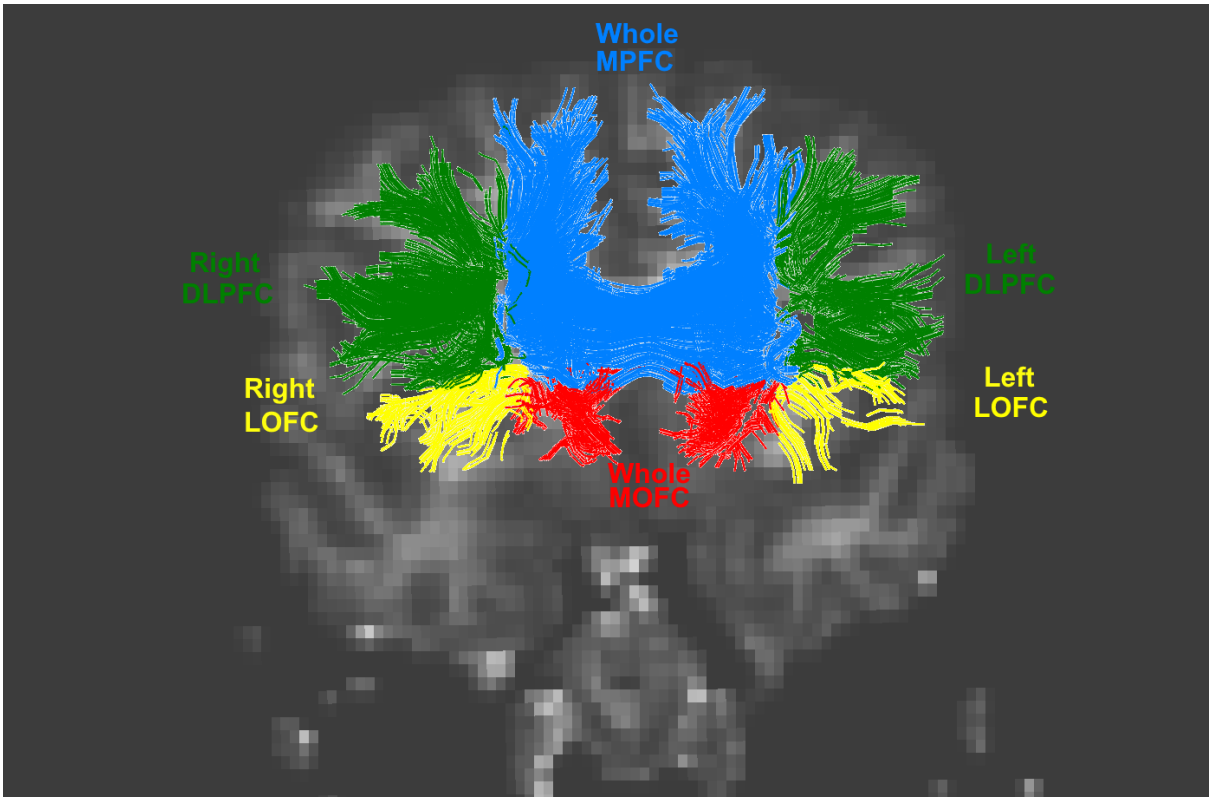

Figure 7. Prefrontal white matter tracts as visualized by diffusion tensor imaging. Color coded tracts are presented in a coronal view. Tracts are named based on the cortical regions they derive from, MOFC: medial orbitofrontal cortex, LOFC: lateral orbitofrontal cortex, MPFC: medial prefrontal cortex, DLPFC: dorsolateral prefrontal cortex.

The reliability of the protocol was determined by two raters (WP and NM), who independently traced all prefrontal subregions in 10 subjects unrelated to this study; intra-rater reliability was obtained by retracing the same subjects within a 1-week interval by a single rater who performed the measurements for the study.

Intraclass correlation coefficients (ICC) were calculated via a mixed effects model, ICC(A,1) as defined by McGraw and Wong (McGraw & Wong, 1996), wherein both the variance between the raters and the variance between their observations were considered; this ICC applied to single measurements and an absolute agreement definition was used. ICCs > 0.80, which indicate excellent agreement between ratings, were achieved for all parameters measured (Table 2) Manual segmentation of all 140 subjects used in this study was performed by a single rater (WP) who was blind to subject age and other demographic information.

	MOFC callosal		MOFC non callosal		LOFC	
	Interrater ICC	Intrarater ICC	Interrater ICC	Intrarater ICC	Interrater ICC	Intrarater ICC
FA	0.982	0.996	0.940	0.933	0.877	0.973
Mean Diffusivity	0.962	0.978	0.924	0.948	0.966	0.993
Axial Diffusivity	0.979	0.973	0.876	0.895	0.994	0.981
Radial Diffusivity	0.968	0.989	0.958	0.984	0.938	0.988
Fiber Count	0.991	0.995	0.974	0.917	0.990	0.957
Fiber Length	0.987	0.995	0.934	0.964	0.916	0.971
Number of voxels	0.989	0.986	0.966	0.955	0.989	0.946

	MPFC callosal		MPFC non callosal		DLPFC	
	Interrater ICC	Intrarater ICC	Interrater ICC	Intrarater ICC	Interrater ICC	Intrarater ICC
FA	0.989	0.990	0.921	0.996	0.976	0.995
Mean Diffusivity	0.991	0.991	0.956	0.993	0.993	0.982
Axial Diffusivity	0.995	0.998	0.966	0.989	0.969	0.996
Radial Diffusivity	0.980	0.988	0.921	0.996	0.996	0.995
Fiber Count	0.991	0.981	0.912	0.883	0.934	0.932
Fiber Length	0.995	0.998	0.911	0.974	0.962	0.971
Number of voxels	0.986	0.991	0.923	0.902	0.890	0.876

Table 2. Reliability Results

Key: FA: Fractional Anisotropy, ICC: intraclass correlation coefficient

2.4. Cognitive Testing

Participant cognitive abilities were evaluated using neuropsychological tests sensitive to aging and linked with PFC functioning. Executive functions were examined using the Delis-Kaplan Executive Functions System (D-KEFS; Delis *et al.*, 2001). Scores from subtest conditions which specifically tap into EFs were selected; including, the Number-Letter Switching condition of the Trail Making Test (TMT-NLS), the Inhibition (CWI-I) and Inhibition-Switch scores (CWI-IS) from the Color-Word Interference Test (CWI), Letter Fluency (VF-LF), Category Fluency (VF-CF), Category Switch (VF-CS), and Category Correct (VF-CC) scores from the Verbal Fluency Test, and Free Sort (Sort-FS), Sort Description (Sort-SD), and Recognition Description (Sort-RD) scores of the Sorting Test. The TMT-NLS, CWI-I, and CWI-IS are all timed scores measuring the seconds it took to perform the task. The TMT-NLS is a visuomotor sequencing task where participants complete a connect-the-circles task alternating between digits and letters, the CWI-I score reflects the time to complete a classic Stroop Test (Stroop, 1935), while CWI-IS is a more challenging Stroop Test that includes another inhibitory rule the participant must consider. The Verbal Fluency Test asks participants to list as many words that satisfy a certain condition in sixty seconds, these conditions are words that start with a specific letter (VF-LF), or satisfy a category such as clothing, animals, or names (VF-CF). The VF-CC and CF-CS scores are derived from a switch condition requiring participants to alternate between two different categories, with VF-CC representing total correct score from either category while VF-CS scores for correct switches only. The D-KEFS Sorting Test is a modified version of the California Card Sorting Test (Delis *et al.*, 1992) which asks the participant to sort sixteen cards into two groups based on perceptual or verbal elements on the card. The test returns separate measures for sort generation (Sort-FS), sort explanation (Sort-SD), as well as a score for examiner prompted sort recognition (Sort-RD). 115 of the 140 participants who underwent scanning also completed the full D-KEFS battery, missing data is random, although disproportionately male (18 male to 7 female) and slightly skewed toward older participants (mean age 49.7). All D-KEFS scores were standardized to Z-score values; since high values on the timed scores of TMT-NLS, CWI-I, and CWI-IS reflect poorer performance, these Z-scores were inverted to match the direction of the other D-KEFS scores. Performance on the D-KEFS battery was assessed as a function of age; scores were therefore not normalized based on the age-adjusted scores contained within the appendix.

To assess memory performance, participants were administered the Wechsler Memory Scale, fourth edition (WMS-IV; Wechsler, 2009). The WMS-IV is a neuropsychological battery consisting of various tests used to evaluate episodic memory, visuospatial memory, and visual working memory. Episodic memory is tested by the logical memory (LM) and verbal paired associates (VPA) subtests, which require examinees to reproduce oral stories and eight verbal word pairs, respectively. Visuospatial memory is evaluated using the Designs (DE), which requires subjects to recall locations of multiple abstract symbols on a spatial grid. The episodic and visuospatial memory tests each have three scores attributed to them, an immediate recall score (marked as 1, eg. LM1), a 25-30 minute delayed recall score (marked 2), as well as a delayed recognition paradigm, in which participants pick the correct answer from a list (marked R). Immediate and delayed tasks measure distinct processes, delayed tasks require memory consolidation, retrieval, and re-encoding compared to the immediate encoding focus of the immediate recall tasks. These subtests are not independent, as immediate recall precedes delayed recall and naturally predicts delayed recall performance while the reverse is not true (Haaland *et al.*, 2003). Delayed recall tasks are more difficult and are believed to be associated more with medial temporal lobe structures compared to the greater frontal dependence on encoding and immediate recall ability (Rosen *et al.*, 2002; Travis *et al.*, 2014). We notably excluded the Visual Reproduction subset of the WMS as a measure of visuospatial memory. The exclusion was predominantly due to large ceiling effects found in the data, with many participants achieving high or perfect scores regardless of age. Ceiling effects for these scores have been reported before (Uttl, 2005) and are an inherent limitation of performing neuropsychological assessment in healthy populations. The remaining visual working memory domain of the WMS-IV comprises two subtests, Spatial Addition (SA) and Symbol Span (SSP), which require the examinee to perform simple arithmetic involving objects placed on a spatial grid (SA) and memorize the sequential order of multiple abstract symbols presented on a page (SSP). Both subtests consist of only one immediate recall score. As with the D-KEFS, WMS-IV scores were standardized to Z-scores and not adjusted for age. Eight participants (2 female, 6 male; mean age 60) did not complete a full WMS-IV battery and were excluded from analysis.

As WM degeneration may be especially susceptible to tasks reliant on speed (Walhovd & Fjell, 2007), participant reaction times were also evaluated. Simple (SRT) and choice (CRT) reaction time measures were obtained using the Deary-Liewald Reaction Time Task (Deary *et al.*, 2011).

The computer-based task requires participants to press the appropriate keyboard key as quickly as possible following the flashing of an 'X' on the screen. In SRT, one X appears and one key is pressed; in CRT, the X may appear at four different locations coded to four different keys, the participant must first accurately determine which key to press based on the location of the stimulus. Both SRT and CRT tests involve twenty trials, with an inter-stimulus interval varying between 1000-3000ms and a response range of 150-1500ms. The mean reaction time across the twenty trials is recorded. Of the 140 participants tested, four participants were removed as outliers leaving 136 for analysis.

Participant processing speed and attention was further evaluated using the Paced Auditory Serial Additions Test (PASAT; Gronwall, 1977). Participants are tasked with listening to a recording of single digits read aloud 3 seconds apart and add each new digit to its predecessor. Participants are scored on the total correct calculations performed out of sixty.

Theory of mind was tested with the Reading the Mind in the Eyes Test (RMET; Baron-Cohen *et al.*, 2001). The test shows pictures of adult eyes while various emotions are being expressed. Participants pick the expression conveyed in the eyes out of a list of 4. Participants are scored based on their accuracy at determining the expressions in the images out of a total of 36.

2.5. Regression Modeling of Age-DTI Relationships

Descriptive and inferential statistics, including data quality control was performed using SPSS (v26; IBM Inc., Armonk, NY). Preliminary analyses involved generating correlation matrices and general linear models to assess the relationships between demographic variables, DTI parameters, and cognitive scores. SPSS is limited in applying an empirical, statistics-driven, approach to finding the best fitting regression model to explain relationships between variables, especially polynomial regressions without a priori exponent selection.

Higher order polynomial regression (HO) models are multiple regression models which may include multiple, higher order, powers of age alongside other demographic variables. Unlike simple, lower order, regression models which impose shape restrictions that may misrepresent findings (Fjell *et al.*, 2010), higher order models allow for more flexible data fitting (Malykhin *et*

al., 2017). Higher order regressions were generated utilizing R (v3.6.1; R Foundation for Statistical Computing, Vienna, Austria). The method used to generate the statistically optimal regression model for the relationship between age and tract-specific characteristics was adapted from previous work in our lab (Pietrasik *et al.*, 2020). Unlike this previous study where HO model fits were statistically compared to LO and linear fits, only the best fit models were presented in this study. To find the variables and powers of age that best explain the variance in tract characteristics we utilized the Bayesian Information Criterion (BIC) selection criterion. The variables considered by BIC during model selection, in addition to the powers of age, were sex, years of education, handedness, and ICV; since the data contained significant interactions between the age, sex, and ICV variables, the age*sex, sex*ICV, and age*sex*ICV interaction terms were also included as potential variables during model selection. The adjusted R^2 of each polynomial model, alongside the *p*-value of total model fit, were reported in the results; *p*-values indicating significance of additional non-age parameters within the model were reported where applicable.

Tracts with separate hemispheric components were extracted separately during tractography, these included the left and right LOFC, DLPFC, and non-callosal portions of the MOFC and MPFC. To determine whether the tracts exhibited significant hemispheric differences, 2-samples t-tests (and non-parametric 2-sample t-tests) were used. In addition, the laterality effect was also tested using a generalized least squares model that accounted for the effect of age, sex, and both age and sex. Tracts that did not exhibit significant differences had their parameters averaged to simplify analysis.

2.6. Factor Analysis

To simplify D-KEFS and WMS-IV analysis and control for measure redundancy, factor analysis was performed on select scores from the WMS-IV and D-KEFS batteries to produce more reliable, latent, cognitive constructs. Previous studies investigating associations between DTI parameters and cognitive performance have utilized dimensionality reduction methods to create latent factor scores that better represent various cognitive modalities (Burgmans *et al.*, 2011; Voineskos *et al.*, 2012). With no a priori hypothesis of how cognitive test scores would segregate into factors, factor analysis of our sample was performed in two steps: an exploratory factor analysis to extract a

reasonable factor structure, followed by confirmatory methods to statistically test the construct validity (Fabrigar *et al.*, 1999; Matsunaga, 2010).

Exploratory factor analysis (EFA) was first performed in SPSS using various extraction techniques to observe the consistency in the factors it produced, factors with eigenvalues greater than 1 were considered significant and provided the initial template to use for confirmatory factor analysis. Due to uneven sample sizes resulting from missing values, separate factor analyses were run for D-KEFS and WMS-IV subtests. To ensure good factors given the sample sizes, variables that could not achieve loadings ≥0.45 on any factor were removed from further confirmatory factor analysis (Hogarty *et al.*, 2005).

Confirmatory factor analysis (CFA) of the D-KEFS and WMS-IV factors was performed using IBM AMOS v26, which uses maximum likelihood estimation. Factor orthogonality is not enforced due to wide acceptance that cognitive constructs correlate with eachother (Deary, 2000). D-KEFS and WMS-IV subtest scores were inputted as indicators contributing to a latent factor representing its EFA counterpart. CFA is performed to determine whether the proposed factor structure properly models the observed data, with model fit being evaluated using numerous fit statistics. To ensure a CFA is well-fitting, models typically need to be within a certain range of values, or above/below a particular threshold of these fit statistics. The appropriate thresholds for fit statistics have been debated by several scholars (Browne & Cudeck, 1992; Hu & Bentler, 1999; Marsh *et al.*, 2004) as no unanimous agreement has been reached on precise cutoff values. Fit indices are also subject to fluidity dependent on the complexity of the model. Taking previous research into account, the following cut-off criteria for fit statistics were utilized to consider a model having acceptable fit: Cmin/df < 3; CFI > 0.9; SRMR < 0.09; RMSEA < 0.1. In addition to model fit indices, factors were tested for convergent and divergent validity and reliability; all factors required composite reliability (CR) values > 0.7, average variance extracted (AVE) values > 0.5, and maximum shared variance (MSV) values lower than AVE values with square root of AVE being greater than all inter-construct correlations (Hair Jr *et al.*, 2017). After establishing a well-fitting factor structure, standardized scores of each factor were imputed to use as a single variable during structural equation modelling.

In addition to D-KEFS and WMS-IV scores, a single factor CFA was performed on FA values of all prefrontal tracts to extract their common variance and reduce it into a single latent measure to

be used for further analysis. This measure would be anatomically non-specific, representing a general FA of all prefrontal WM. In addition to its simplicity, the single latent factor would also be more reliable by eliminating the impact of noise or measurement error that may be specific to individual tracts (Gazes *et al.*, 2016). As the purpose of this CFA was to reduce the number of variables, creating a single factor explaining a substantial amount of shared variance at the expense of anatomical specificity is ideal. FA was chosen as the variable of interest as it is the variable most often reported in DTI studies, and due to its tendency to decline linearly with age following adulthood (Hsu *et al.*, 2010; Pietrasik *et al.*, 2020) often a requirement for general linear model (GLM) analyses.

2.7. Structural Equation Modeling

Structural equation modelling based path analyses were used to examine the relationships between demographic variables, white matter microstructure, and cognitive functions, and estimate the size of these effects. More specifically, SEM was used to determine whether age differences in cognitive performance were mediated by white matter degeneration seen in aging, as measured by DTI parameters. Unlike zero order correlations, associations between variables in SEM have directionality which allow for the inference of causal relationships. In addition, while a simple bivariate analysis assumes all predictive variables are independent, SEM involves multivariate analysis that can account for shared variance and correlations between variables leading to more accurate calculation of true effects.

SEM was ran using maximum likelihood estimation in IBM AMOS v26. Models and directional relationships were set up based on theoretical considerations and preliminary correlations. Only significant associations between demographic variables, or variables that were found to be significant predictors of FA or cognitive test scores, were included in SEM analysis. To assess model fit, the same fit statistic thresholds were used as those in CFA: Cmin/df < 3; CFI > 0.9; SRMR < 0.09; RMSEA < 0.1. Calculation of indirect effects and their significance for mediation was performed through bootstrapping using 5000 bootstraps and a 95% percentile bootstrap confidence interval (CI) to minimize type I errors (Hayes & Scharkow, 2013). CIs that did not contain a 0 were reported as significant.

The analysis was performed in two steps:

Step 1: Initial analysis ran each distinct cognitive test or imputed factor in separate SEM models; mediation analysis was first investigated on the global FA parameter calculated during the CFA step. Significant demographic variables, such as age and ICV, were selected as predictors of PFC FA and/or cognitive performance measures, while PFC FA predicted only cognitive measures.

Step 2: This was followed by a separate single subregion mediation analysis, where the general PFC FA variable is replaced with subregion specific FA to further investigate potential anatomic specificity of mediating effects. This was repeated for each subregion and cognitive measure, estimated using the same bootstrap criteria described above.

The direct and indirect effect pathways from general FA and single tract analyses were extracted, with standardized β coefficients, their CIs, and regression R^2 values reported in the results where applicable.

3. Results

3.1. General Results

The study sample shows no significant associations between age, sex, education, or handedness (Table 1); however, an independent sample t-test found men to have larger ICV values [t (138) = 10.88, $p < 0.001$], ICV values in males were also found to decline slightly with increased age (r=-0.29, p=0.023) while the ICV of females remained the same across the lifespan (p=0.763). Therefore, ICV was used as a covariate in our analysis where required. All prefrontal subregions show age differences in WM microstructural properties, with patterns of decrease in FA and increases in MD, AD, and RD with increased age (Tables 3-6). ICV, sex, or interaction terms were also selected as a significant predictor of FA values in certain cases. Prefrontal subregions were not uniformly affected by age in DTI parameters measuring macrostructural properties, such as fiber count, fiber length, and tract volume (Tables 7-10); macrostructural properties were however more sensitive to ICV, with the exception of tract volume which was previously ICV adjusted. To determine the presence of hemispheric differences between the left and right non callosal tracts, a 2 samples t-test was performed. The WM in the MOFC and MPFC is divided into fibers passing through the corpus callosum (MOFCc, MPFCc), and non-callosal WM localized to each hemisphere. No significant differences were found between the right and left subdivisions of non-callosal white matter in any of DTI parameters in these medial tracts. Analysis was performed on the parameter means of the left and right sections together, hereafter referred to as MOFCnc and MPFCnc. In the lateral tracts of the LOFC and DLPFC, some DTI parameters showed evidence of asymmetry when compared with the 2 samples t-test, the WM within these subregions were split into left and right and analyzed separately (designated L or R where applicable). Detailed results from higher order polynomial regression modeling of all DTI parameters studied is separated by parameter in this section.

3.2. Fractional Anisotropy

Fractional anisotropy (FA) of all prefrontal subregions showed declines with age. Model R^2 was lowest in the right LOFC (0.1603) and high (>0.4) in the callosal MPFC, right DLPFC, and MOFCnc (Table 3). The pattern of decline followed a linear trajectory in the LOFCR and the MPFCc, the remaining regions followed quadratic or cubic regressions (Figure 8).

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
FA	MOFC callosal	0.2784	1.264e-11	Quadratic	1.26e-11	-	-
	MOFC non-callosal	0.4937	< 2.2e-16	Quadratic	< 2e-16	Sex ICV*Sex	0.000284 0.000322
	LOFC left	0.2266	8.412e-09	Cubic	3.26e-08	ICV	0.0254
	LOFC right	0.1603	2.353e-06	Linear	1.1e-05	ICV	0.0246
	MPFC callosal	0.4125	< 2.2e-16	Linear	<2e-16	-	-
	MPFC non-callosal	0.3952	< 2.2e-16	Quadratic	<2e-16	-	-
	DLPFC left	0.2906	3.85e-12	Quadratic	3.85e-12	-	-
	DLPFC right	0.4459	< 2.2e-16	Quadratic	1.02e-14	Age*Sex ICV*Sex*age	0.00303 0.00581

Table 3. Associations between age and fractional anisotropy (FA). Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values. *denotes interaction terms

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
MD	MOFC callosal	0.2949	2.507e-12	Quadratic	2.51e-12	-	-
	MOFC non-callosal	0.3145	3.491e-13	Cubic	3.49e-13	-	-
	LOFC left	0.1935	3.216e-08	Quartic	3.22e-08	-	-
	LOFC right	0.1719	2.107e-07	Quadratic	2.11e-07	-	-
	MPFC callosal	0.2956	2.343e-12	Quartic	2.34e-12	-	-
	MPFC Non-callosal	0.2395	5.114e-10	Quintic	5.11e-10	-	-
	DLPFC left	0.2728	1.326e-09	Septic Octic Nonic Decic	0.002758 0.001711 0.001161 0.000832	-	-
	DLPFC right	0.3407	2.264e-14	Quintic	2.26e-14	-	-

Table 4. Associations between age and mean diffusivity (MD). Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values.

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
RD	MOFC callosal	0.3256	1.111e-13	Quadratic	1.11e-13	-	-
	MOFC Non-callosal	0.4115	< 2.2e-16	Cubic	<2e-16	-	-
	LOFC left	0.2688	3.225e-11	Cubic	3.22e-11	-	-
	LOFC right	0.2088	8.346e-09	Quadratic	8.35e-09	-	-
	MPFC callosal	0.353	6.126e-15	Cubic	6.13e-15	-	-
	MPFC Non-callosal	0.3375	3.191e-14	Quartic	3.19e-14	-	-
	DLPFC left	0.2508	1.776e-10	Quartic	1.78e-10	-	-
	DLPFC right	0.3923	< 2.2e-16	Quartic	<2e-16	-	-

Table 5. Associations between age and radial diffusivity (RD). Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values.

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
AD	MOFC callosal	0.1946	2.935e-08	Quadratic	2.93e-08	-	-
	MOFC Non-callosal	0.1173	2.044e-05	Sextic	2.04e-05	-	-
	LOFC left	0.1367	4.118e-06	Quartic	4.12e-06	-	-
	LOFC right	0.1183	1.875e-05	Cubic	1.87e-05	-	-
	MPFC callosal	0.1671	3.184e-07	Septic	3.18e-07	-	-
	MPFC Non-callosal	0.04809	0.005311	Decic	0.00531	-	-
	DLPFC left	0.196	8.852e-07	Septic Octic Nonic Decic	0.000309 0.000260 0.000227 0.000200	-	-
	DLPFC right	0.206	1.067e-08	Septic	1.07e-08	-	-

Table 6. Associations between age and axial diffusivity (AD). Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values.

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
Fiber Count	MOFC callosal	0.07031	0.0009026	Quadratic	0.000903	-	-
	MOFC Non-callosal	0.192	1.681e-07	Quintic	0.00171	ICV	8.63e-06
	LOFC left	0.2177	1.848e-08	Quartic	0.000463	ICV	3.03e-06
	LOFC right	0.1642	1.709e-06	Quartic	0.00275	ICV	6.25e-05
	MPFC callosal	0.3421	1.303e-13	Cubic	2.75e-10	ICV	1.27e-05
	MPFC Non-callosal	0.2597	4.183e-10	Quartic	0.0145	ICV	2.44e-09
	DLPFC left	0.252	8.551e-10	Quintic	0.00742	ICV	9.1e-09
	DLPFC right	0.2494	1.082e-09	Nonic	0.00237	ICV	3.06e-08

Table 7. Associations between age and fiber count. Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values.

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
Tract Volume	MOFC callosal	0.1008	7.809e-05	Cubic	7.81e-05	-	-
	MOFC Non-callosal	0.07571	0.0005864	Quintic	0.000586	-	-
	LOFC left	0.1025	6.807e-05	Quintic	6.81e-05	-	-
	LOFC right	0.0578	0.002447	Sextic	0.00245	-	-
	MPFC callosal	0.275	1.759e-11	Quartic	1.76e-11	-	-
	MPFC Non-callosal	0.1474	1.683e-06	Quartic	1.68e-06	-	-
	DLPFC left	0.06953	0.0009608	Quintic	0.000961	-	-
	DLPFC right	0.08866	0.0002078	Decic	0.000208	-	-

Table 8. Associations between age and tract volume. Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values.

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
Fiber Length	MOFC callosal	0.04371	0.007545	Quadratic	0.00754	-	-
	MOFC Non-callosal	0.1952	1.285e-07	Quartic	9.16e-05	ICV	0.000117
	LOFC left	0.04158	0.008951	Quadratic	0.00895	-	-
	LOFC right	0.05148	0.004051	-	-	ICV	0.00405
	MPFC callosal	0.3395	1.697e-13	Quartic	3.84e-10	ICV	1.17e-05
	MPFC Non-callosal	0.3397	1.666e-13	Quintic	1.56e-09	ICV	2.42e-06
	DLPFC left	0.1851	8.86e-07	-	-	Age*Sex ICV ICV*Sex	3.19e-05 0.00105 1.62e-06
	DLPFC right	0.1157	8.155e-05	Quartic	0.00129	ICV	0.00770

Table 9. Associations between age and fiber length. Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values. Key: ICV: intracranial volume. *denotes interaction terms

Parameter	Region	Adjusted R^2	Model *p*-value	Power(s) of Age	Age p-value	Other Variables	Other variable p-value
Fibers Per Voxel	MOFC callosal	0.02053	0.04987	Linear	0.0499	-	-
	MOFC Non-callosal	0.06142	0.001833	Sextic	0.00183	-	-
	LOFC left	0.09069	0.0005504	Linear	0.02152	ICV	0.00354
	LOFC right	0.1169	0.0001736	Nonic Decic	0.000541 0.000643	ICV	0.006020
	MPFC callosal	0.2369	3.34e-09	Cubic	2.48e-08	ICV	0.0121
	MPFC Non-callosal	0.05951	0.002136	-	-	ICV	0.00214
	DLPFC left	0.1141	0.0002133	-	-	ICV ICV*Sex	0.000698 0.001625
	DLPFC right	0.1184	6.586e-05	Quintic	0.00308	ICV	0.00252

Table 10. Associations between age and fibers per voxel. Additional variables contributing to the best-fit models are displayed in the 'Other variables' column alongside their *p*-values. Key: ICV: intracranial volume. *denotes interaction terms

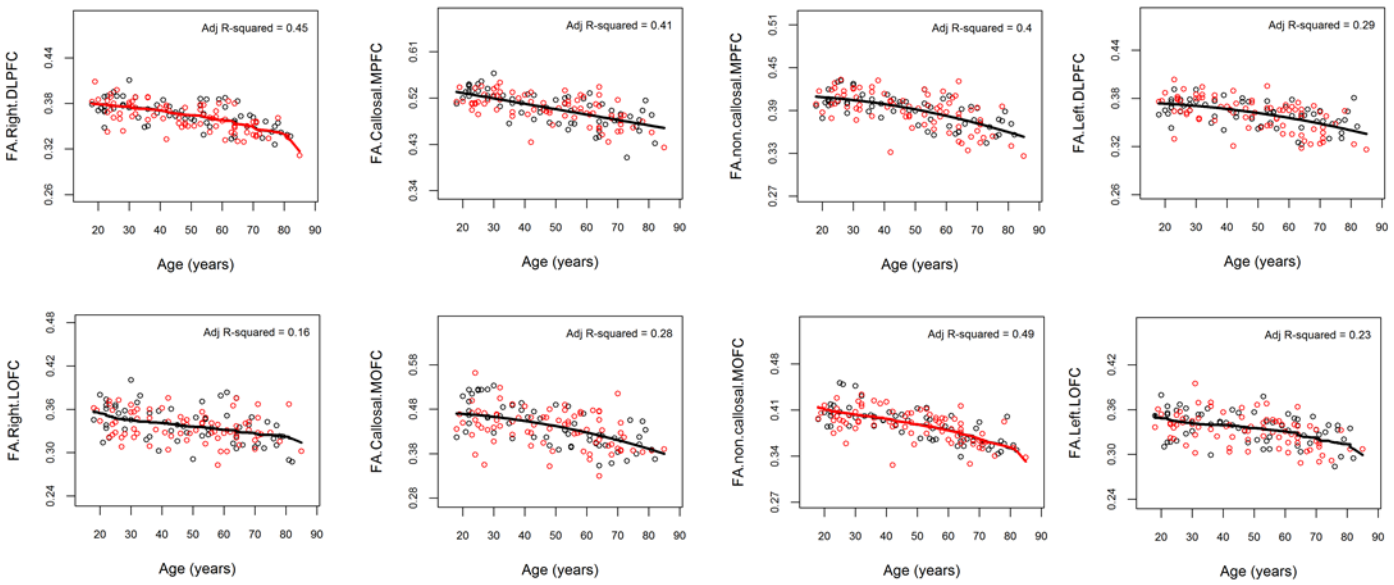

Figure 8. Associations between fractional anisotropy (FA) and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age. Parameters with significant sex, or sex interaction, effects have separate regression curves for males and females to illustrate this interaction.

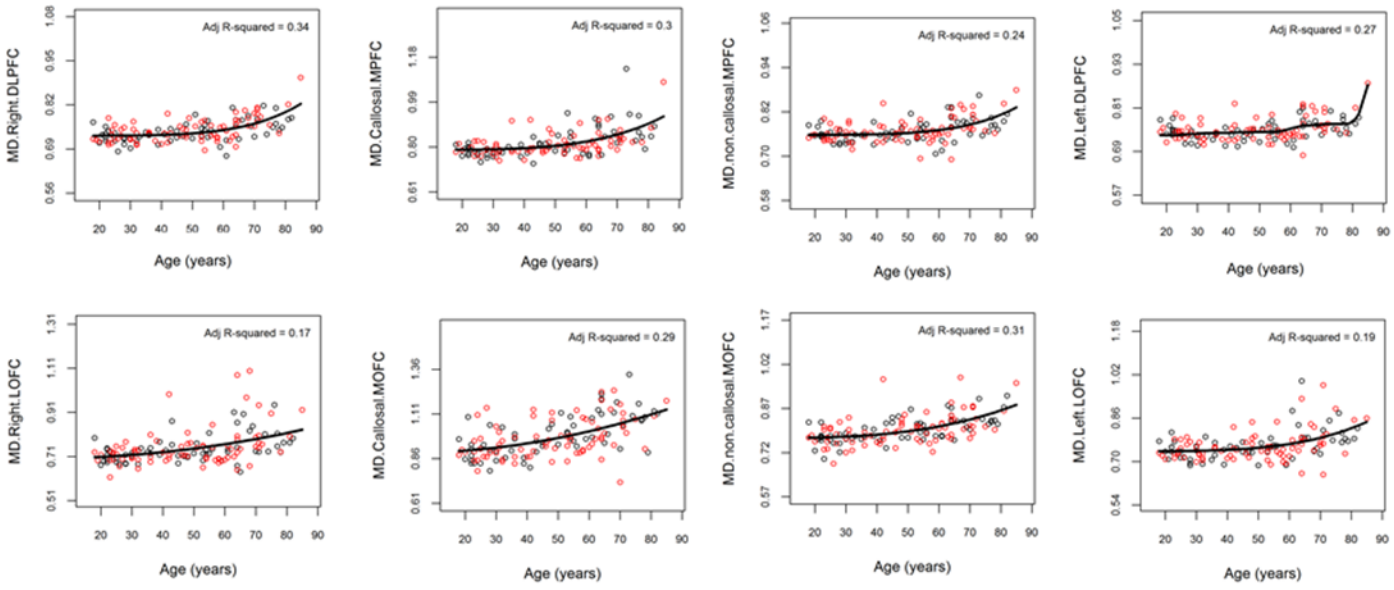

Figure 9. Associations between medial diffusivity (MD) and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age.

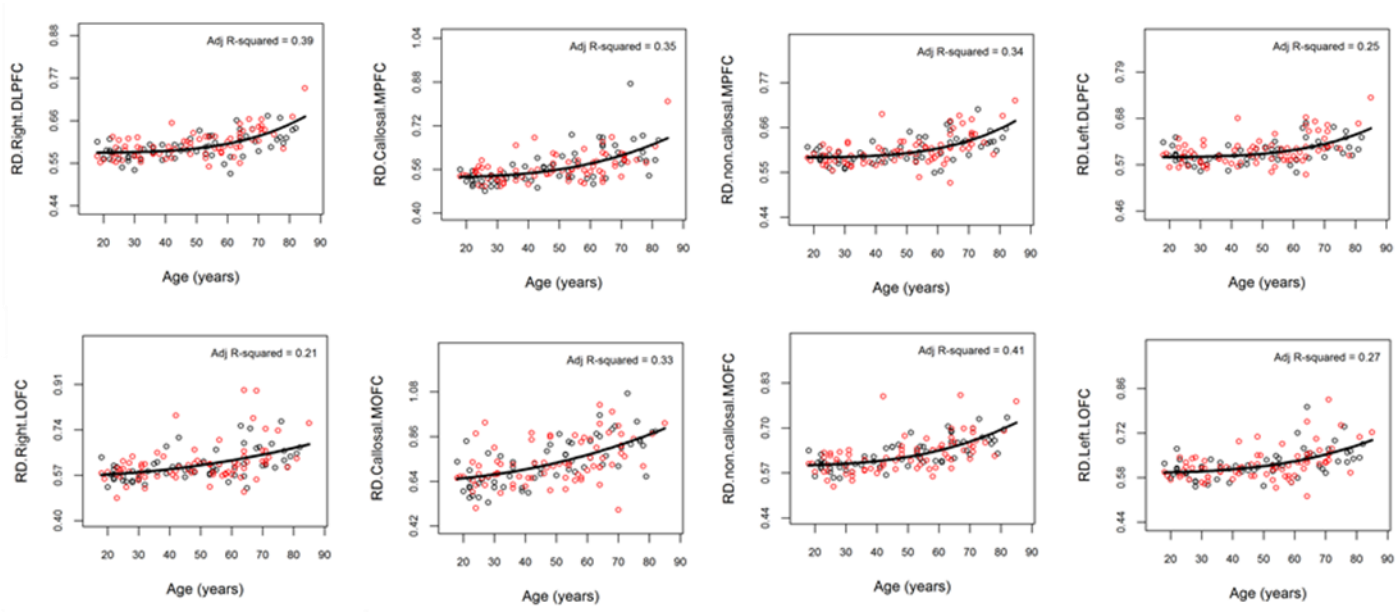

Figure 10. Associations between radial diffusivity (RD) and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age.

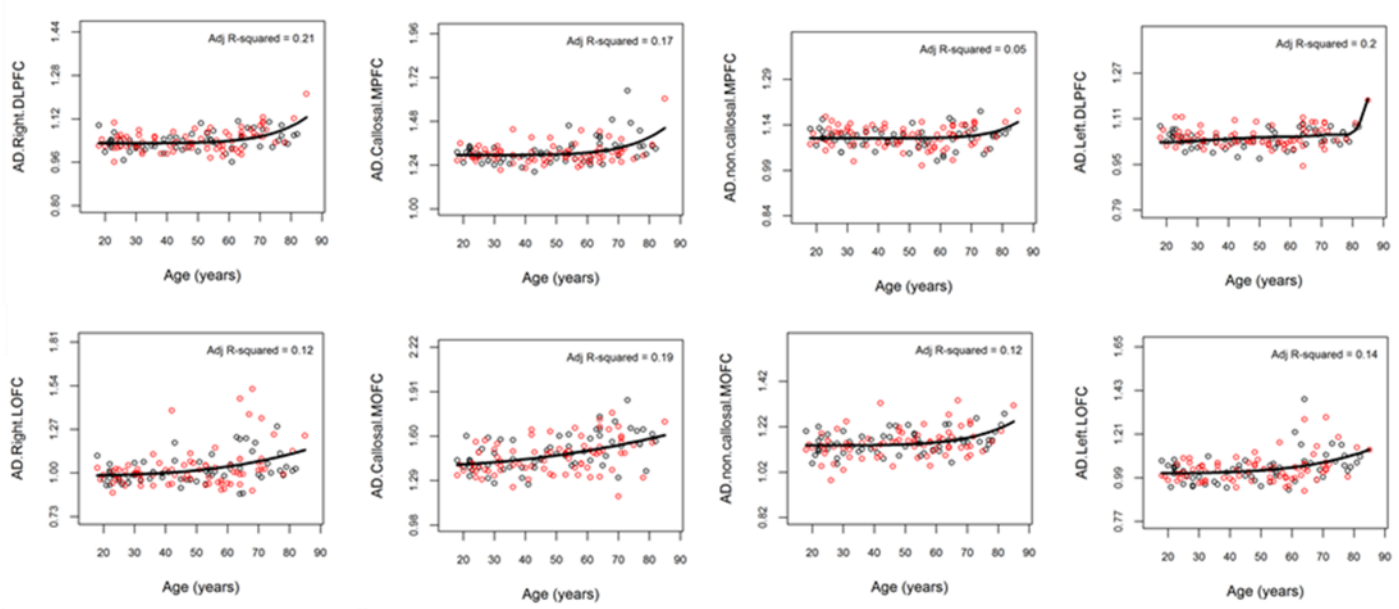

Figure 11. Associations between axial diffusivity (AD) and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age.

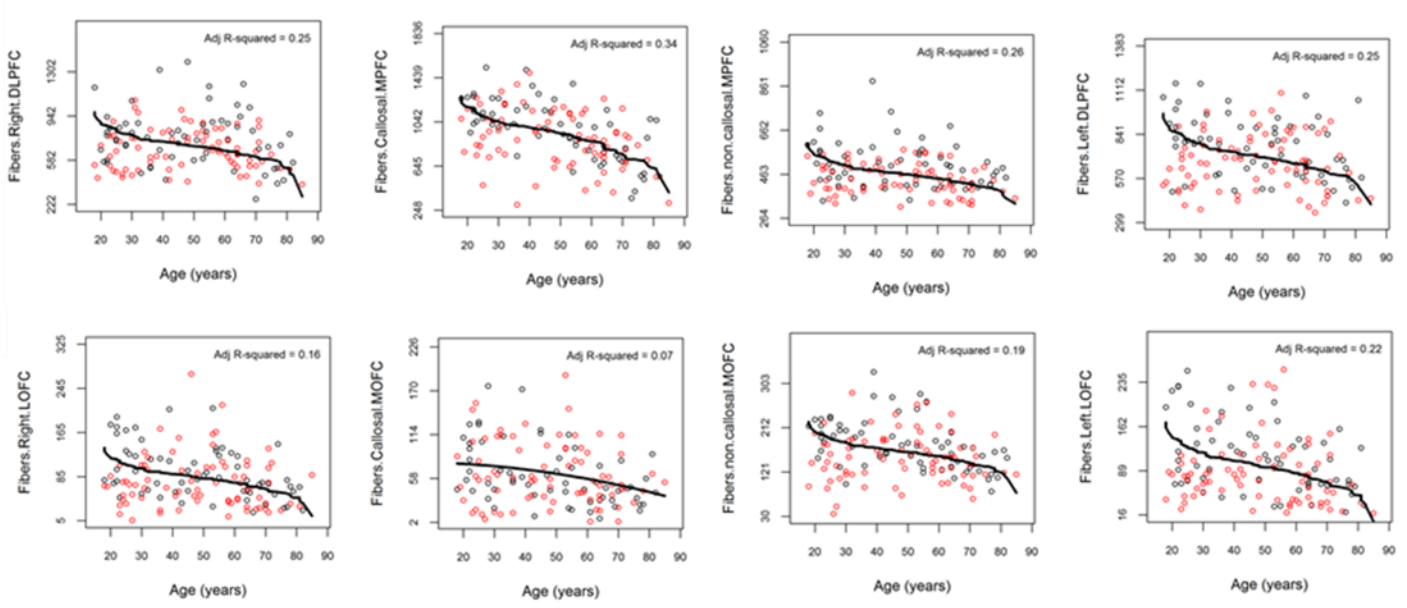

Figure 12. Associations between fiber count and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age.

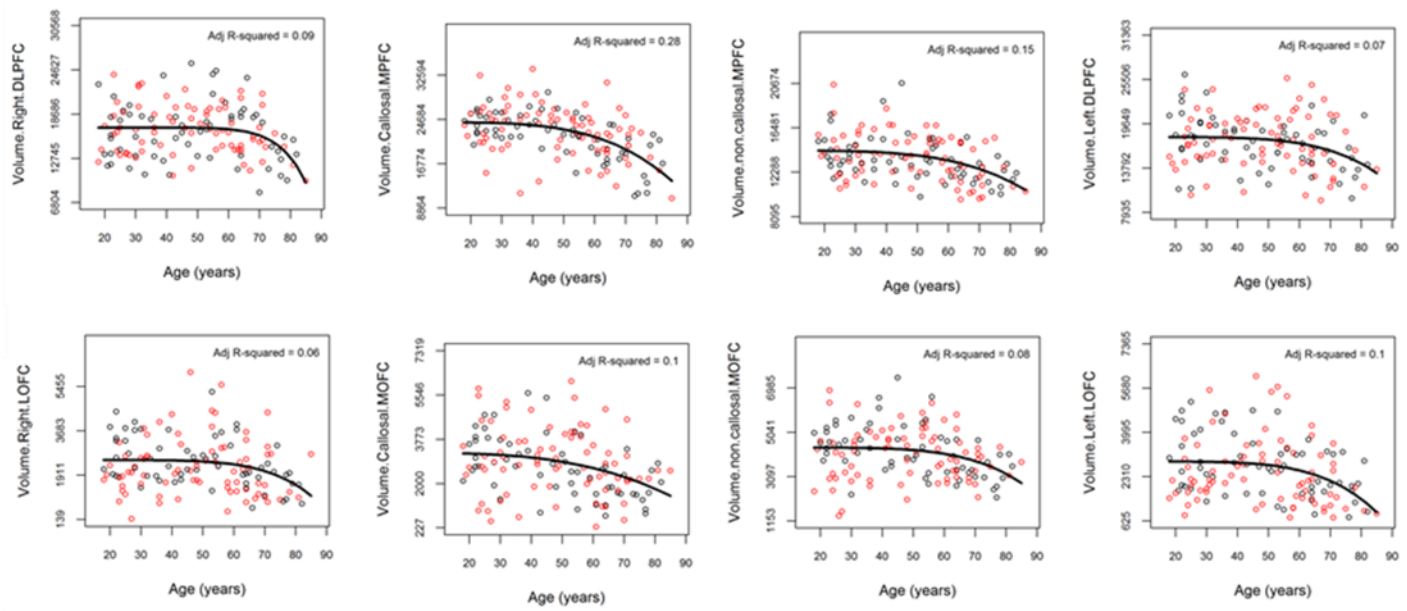

Figure 13. Associations between tract volume and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age.

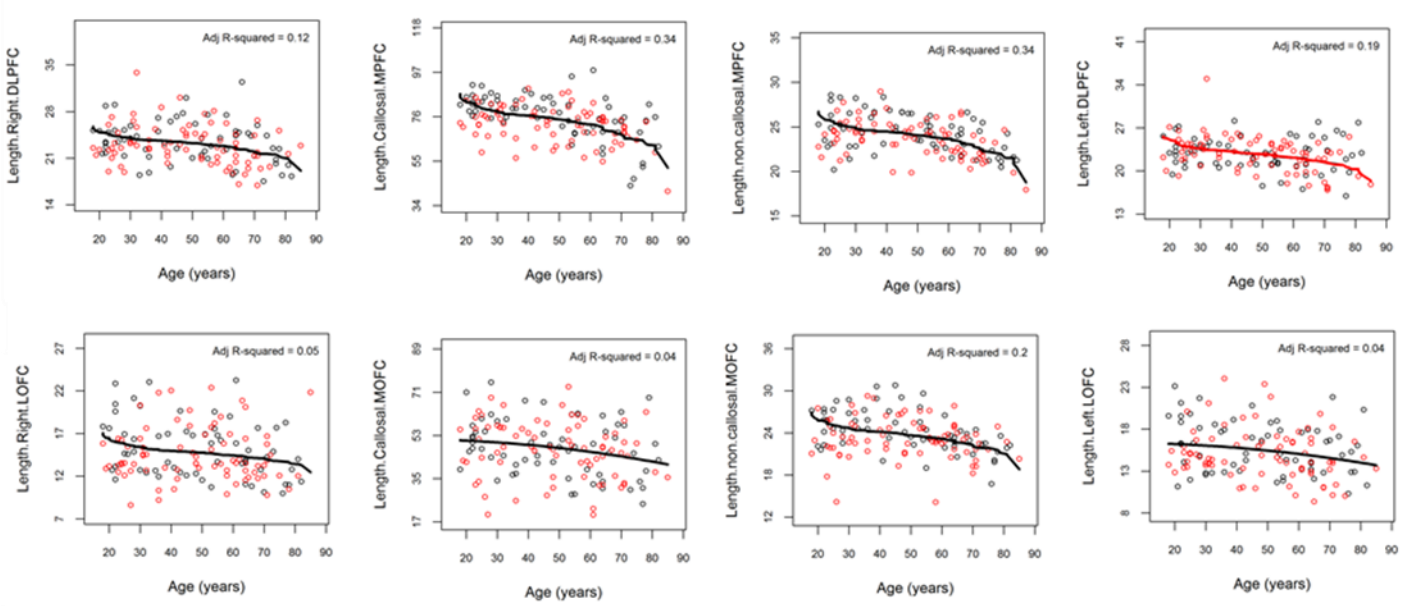

Figure 14. Associations between fiber length and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age. Parameters with significant sex, or sex interaction, effects have separate regression curves for males and females to illustrate this interaction.

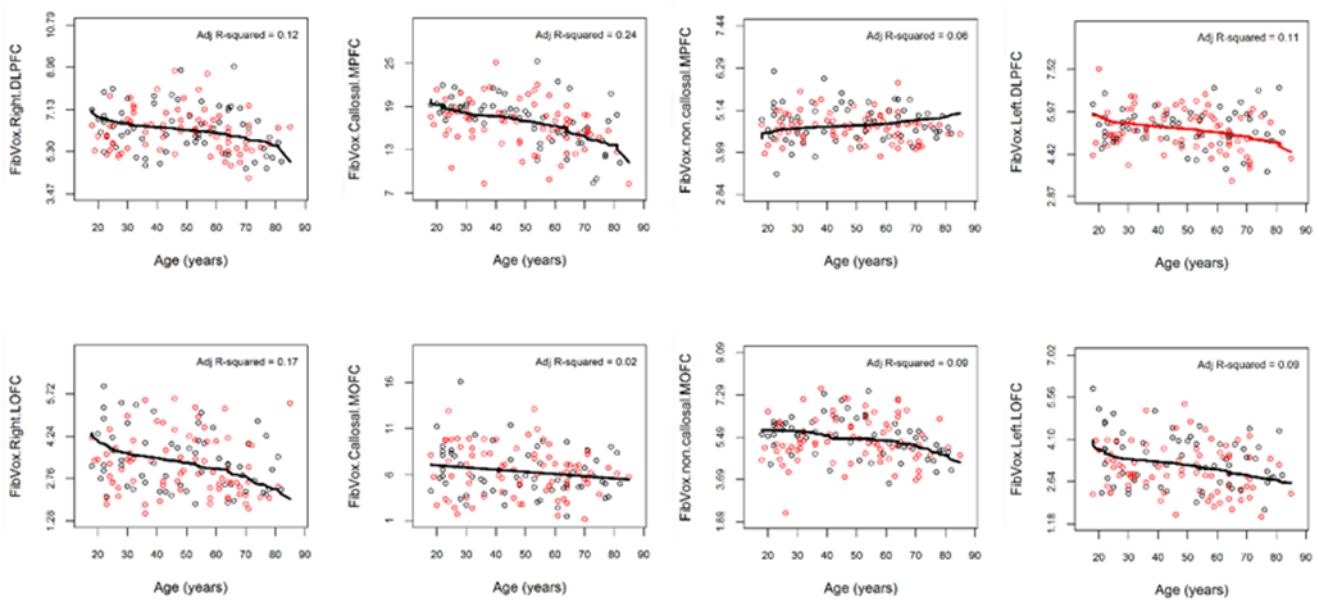

Figure 15. Associations between fibers per voxel (Fibvox) and age. Black circles represent males and red represent females. Trendlines represent higher order regression estimations of the decline trajectory that occurs with advancing age. Parameters with significant sex, or sex interaction, effects have separate regression curves for males and females to illustrate this interaction.

3.3. Diffusivity Measures

Mean diffusivity (MD) was positively associated with age, with the strongest effects of age in the right DLPFC and the weakest in the right LOFC (Table 4). All relationships follow non-linear trajectories (Figure 9), with the DLPFCL being best characterized by a multifactorial polynomial model that included the 7^{th}, 8^{th}, 9^{th}, and 10^{th} powers of age.

Increased age resulted in a rise in the radial diffusivity (RD) values of all prefrontal subregions, with the strongest effect in the MOFCnc and the weakest in the LOFCR (Table 5). All relationships were non-linear in nature, following a quadratic, cubic, or quartic regression (Figure 10).

Axial diffusivity (AD) increased with age in all prefrontal subregions with relatively small effect sizes (Table 6). A significantly marginal effect was found in the MPFCnc (R^2 =0.04809), with the DLPFCR showing the largest effect of age (R^2 = 0.206). All relationships were non-linear (Figure 11) and all but one model chose a HO polynomial regression. Similar to MD, AD of the DLPFCL selected a multifactorial model.

3.4. Macrostructural Measures

Fiber count decreased in all prefrontal subregions with increased age (Table 7). The effects were marginal in the MOFCc (R^2 = 0.07031) and most prominent in the MPFCc (R^2 = 0.3421). All models contained a power of age, demonstrating the universal non-linearity of the age-fiber count relationship (Figure 12). Tract volumes decreased non-linearly with increased age in all prefrontal subregions (Table 8). The effect sizes were relatively small in most cases ($R^2 \leq 0.1$), with the exception of the callosal and non-callosal MPFC tracts (R^2 of 0.275 and 0.1474, respectively). Average fiber length declined with age in all regions but the LOFCR and the DLPFCL, where no significant relationships with age were found (Table 9). In these regions, BIC chose other variables aside from age to create a significant model. All significant patterns with age were nonlinear (Figure 14), with the strongest age effects in both MPFC tracts, and weak in the MOFCc and both LOFC tracts. The average fibers per voxel of the tract decreased with age in all prefrontal subregions but the MPFCnc and the DLPFCL (Table 10), while the effect of age on the MOFCc is marginally significant (p=0.049). The decline in the MOFCc and LOFCL is best described as

linear, all other regions show nonlinear declines with age, with the LOFCR producing a multifactorial model. The effects of age were strongest in the MPFCc.

3.5. Effects of Sex and ICV

In several DTI parameters, BIC chose sex, ICV, or specific interaction terms as significant predictors in the multivariate model. This occurred in the macrostructural measures of Fiber Count, Fiber Length, and Average Fibers per Voxel, as well as FA. Tract volume was noticeably spared due to being previously adjusted for individual ICV values; in addition, MD, AD, and RD were not influenced by sex, ICV, or any interaction terms.

In FA, 4 prefrontal subregions included terms other than age in the model. Interindividual differences in the non-callosal MOFC were also influenced by a significant sex difference and significant sex*ICV interaction, wherein males had higher FA values than women, and a lower ICV was associated with lower FA values in men with no ICV effect in women. Differences in LOFC FA were also significantly predicted by subject's ICV, where a larger ICV was associated with a higher average FA. The right DLPFC had the additional variables of age*sex and ICV*age*sex interactions as significant in the model, showing that females experience a more pronounced decline in FA generally; while in men, the reductions in ICV with age are linked with age-related decreases in FA.

Fiber count was significantly influenced by ICV in all prefrontal subregions but the callosal MOFC (Table 7), greater ICV was associated with a larger fiber count. ICV produced a similar effect on average fiber lengths, with greater ICV values predicting longer average fibers in all regions but the callosal MOFC and the left LOFC.

Although age was not a significant predictor of fiber lengths in the left DLPFC, age*sex and ICV*sex terms were significant predictors alongside ICV, indicating that age related decline occurs in women but not men, and that the effect of ICV on fiber length of this region is more pronounced in women.

The average fibers per voxel of each tract was significantly predicted by ICV in all prefrontal subregions but the callosal and non-callosal MOFC tracts, with larger ICV predicting greater

values. The left DLPFC also included the ICV*sex term, where the effects of ICV were significantly more pronounced in women rather than men.

Despite covariance between sex and ICV, BIC notably chose ICV, and not sex, as the secondary predictor of DTI parameters in most cases. Although significant covariance exists between sex and ICV, it is the inclusion of ICV that led to greater model fit and a lower BIC. Once ICV is added, sex is not added as a significant predictor in the model alongside it, suggesting that the interindividual differences in DTI values are due more so to ICV rather than sex.

3.6. Factor Analysis

Exploratory factor analysis of the 10 D-KEFS subtests returned a four factor structure (Figure 16). The first factor, with high loadings from all 3 subscores of the card sorting test, was named Conceptual Flexibility; the second factor, named Inhibition, was comprised of the TMT-NLS and both CWI scores. The VF test was split into two factors, Verbal Switch, which included the VF-CC and VF-CS scores, and Verbal Fluency which was heavily loaded by the VF-LF and VF-CF subscores. These four factors were transferred to a CFA, which calculated the factor structure as having acceptable fit (Cmin/df = 2.078; CFI= 0.965; SRMR=0.085; RMSEA=0.097). The factors had no concerns with reliability, convergent validity, or divergent validity (lowest CR= 0.760, lowest AVE= 0.554, highest MSV= 0.259). The initial EFA of WMS-IV scores produced 3 factors with eigenvalues greater than 1 (Figure 17); however, VR subtests exhibited both significant cross-loading between factors and factor loadings under the 0.45 threshold. Cross loadings were eliminated upon removal of VR scores from the EFA and a three factor structure was extracted. The first factor represented Visuospatial Memory, with high loadings from DE, SA, and SSP scores. The second factor, Logical Memory, was comprised of all LM scores, and the third factor, Verbal Memory, was composed of the three VPA scores.

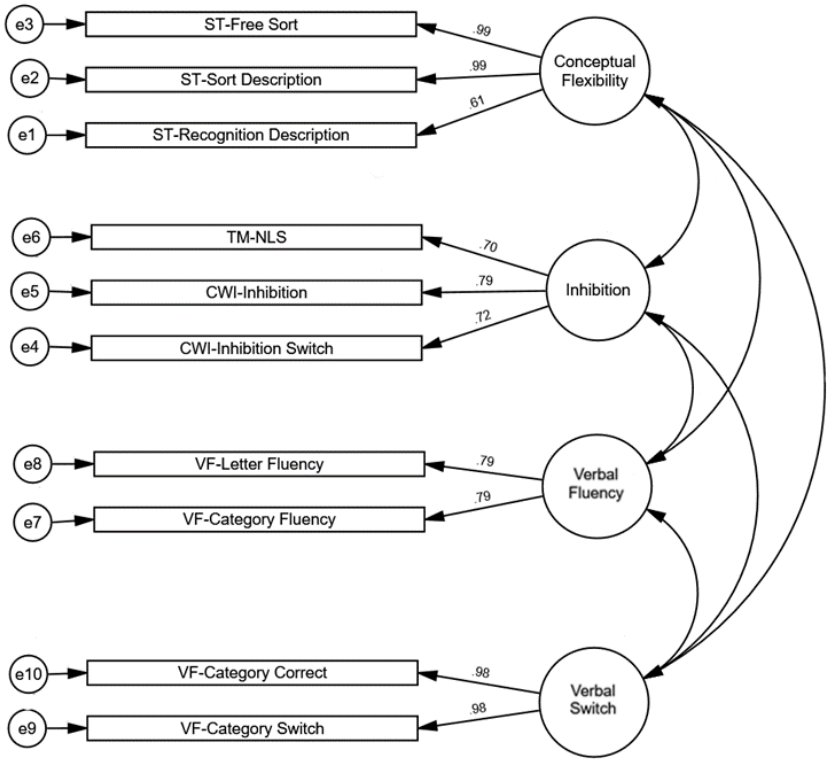

Figure 16. Confirmatory factor analysis of D-KEFS scores. CFA generated four factors out of 10 D-KEFS scores. Numbers indicate loadings of each individual test to that factor.

The three factors were tested for fit using CFA (Figure 17), which showed the factor structure had excellent fit (Cmin/df = 1.197; CFI = 0.991; SRMR = 0.046; RMSEA = 0.039). The factor structure also demonstrated good reliability, convergent validity, and divergent validity (lowest CR = 0.766, lowest AVE = 0.797, highest MSV = 0.728).

The CFA of the general prefrontal FA latent factor, indicated by the FA values of all measured prefrontal subregions (Figure 18), showed adequate fit (Cmin/df = 2.103; CFI = 0.981; SRMR = 0.05; RMSEA = 0.089). Attempts to separate prefrontal WM into further divisions such as orbitofrontal-prefrontal or medial-lateral results in a failure for the model to attain discriminant validity. Since a composite measure of all FA values can be obtained, this factor can be utilized in the general first step SEM.

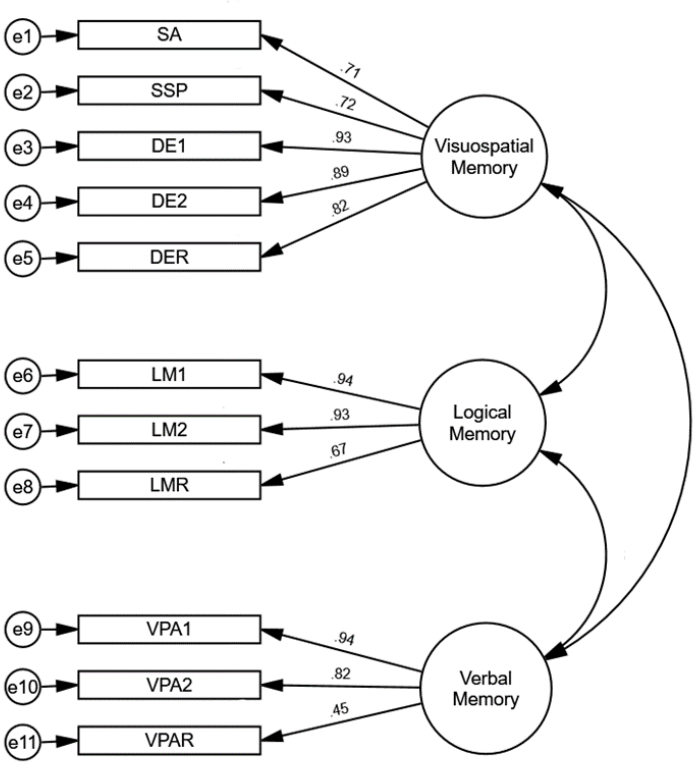

Figure 17. Confirmatory factor analysis of WMS-IV scores. CFA generated three factors out of 11 WMS-IV scores. Numbers indicate loadings of each individual test to that factor.

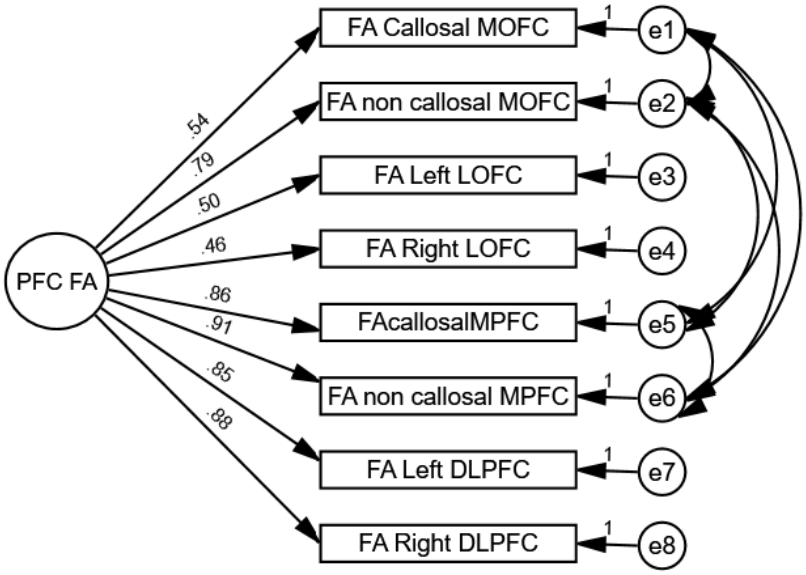

Figure 18. Confirmatory factor analysis of a general FA factor. FA values from all tracts were selected as indicators for a global PFC FA measure. Numbers indicate loadings of each region to the factor. The error variances of all medial tracts were covaried to achieve fit.

3.7. Associations between Demographics and Cognitive Functions

Structural equation models were generated, in part, based on the initial relationships found between demographic variables such as age, sex, and ICV, and cognitive performance scores. These simple Pearson correlations, termed zero-order correlations, do not account for covariances that may exist between the predictor variables; significant results are summarized in Table 11.

Preliminary zero-order Pearson correlations showed that increased age was associated with decreased scores on all three WMS-IV factors (Figure 19); D-KEFS factor scores in Conceptual Flexibility, Inhibition, and Verbal Switch also decreased with age while Verbal Fluency was unaffected by age (Figure 19). PASAT scores also declined with age (Figure 22), while mean SRT and CRT increased with age (Figure 21). RMET scores were not affected by age.

In addition to significant effects of age, Verbal Switch scores also exhibited sex differences, with higher average scores in women; a sex effect was also recorded in PASAT scores with higher average scores in men compared to women. The only variable with a significant effect of ICV was PASAT, where higher ICV predicted higher scores. SRT was also linked with years of education, with greater education predicting faster reaction times.

Cognitive Test	Zero order correlation	Pearson coefficient	p-value
Conceptual Flexibility	Age->Conceptual Flexibility	-0.421	3E-6
Inhibition	Age->Inhibition	-0.624	9.64E-14
Verbal Switch	Age->Verbal Switch	-0.221	0.018
	Sex->Verbal Switch	0.197	0.035
Visuospatial Memory	Age->Visuospatial Memory	-0.782	1.7E-28
Logical Memory	Age->Logical Memory	-0.325	1.43E-4
Verbal Memory	Age->Verbal Memory	-0.648	4.36E-17
SRT	Age->SRT	0.387	3E-6
	Years of Education->SRT	-0.250	0.003
CRT	Age->CRT	0.689	1.89E-20
PASAT	Age->PASAT	-0.199	0.018
	Sex->PASAT	-0.181	0.032

Table 11. Significant zero order correlations between demographic variables. Demographic variables include age, sex, intracranial volume (ICV), and years of education and cognitive scores. Sex effects indicate women perform better on Verbal Switching an worse on PASAT compared to men.

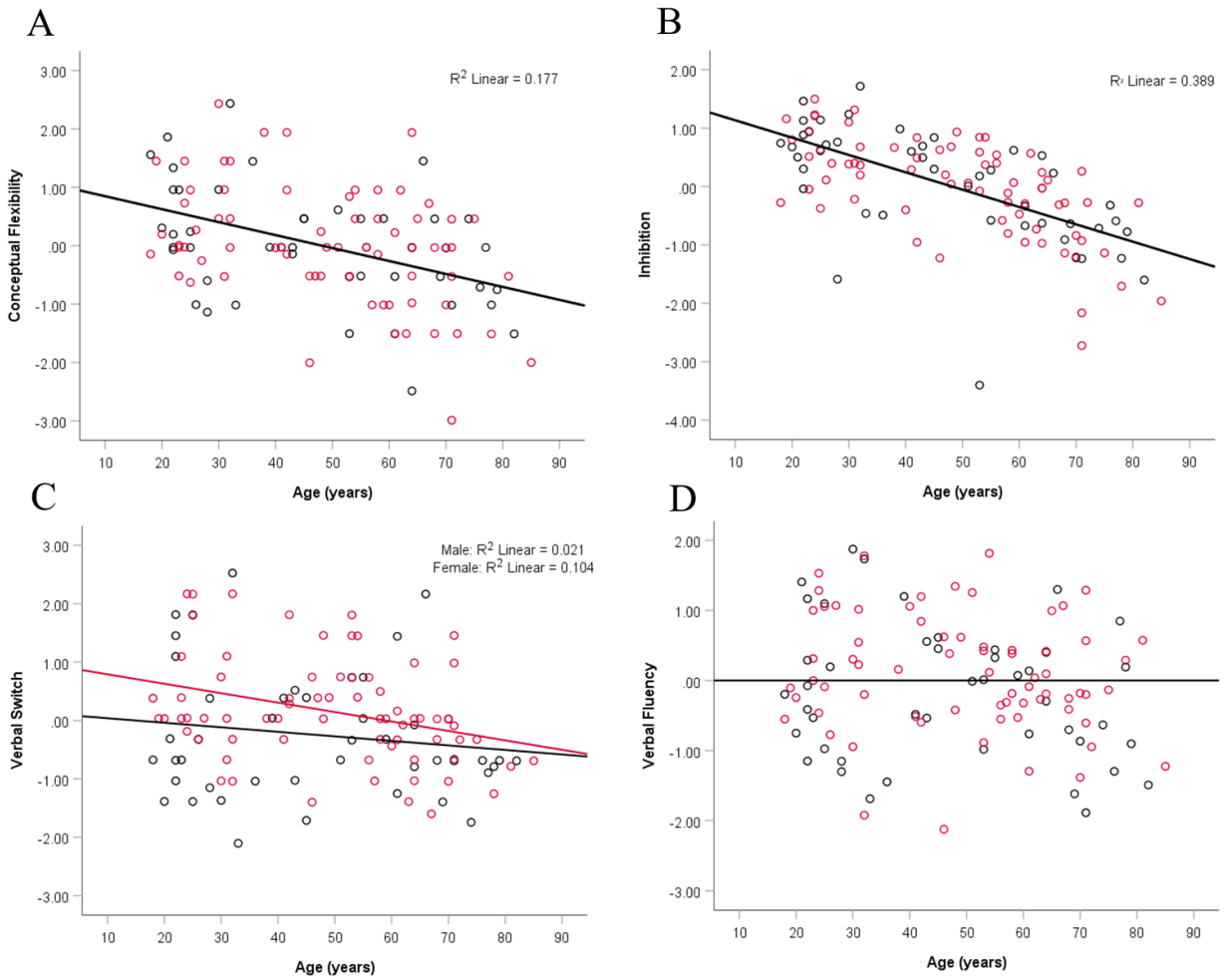

Figure 19. Simple correlation scatterplots between age and D-KEFS factor scores. Conceptual Flexibility (A), Inhibition (B), Verbal Switch (C), and Verbal Fluency (D) zero order correlations with age are visualized using scatterplots. As Verbal switch also has a significant effect of sex, separate trendlines for males (black) and females (red) were drawn. Verbal Fluency has no significant effect of age.

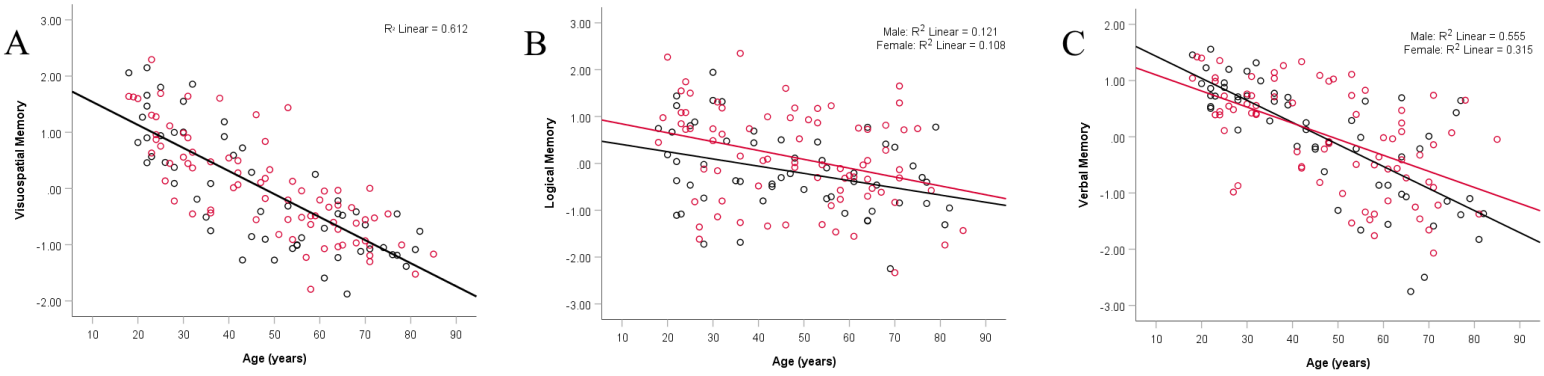

Figure 20. Simple correlation scatterplots between age and WMS-IV factor scores. Visuospatial Memory (A), Logical Memory(B), and Verbal Memory (C) zero order correlations with age are visualized using scatterplots. Logical and verbal memory also had significant associations with sex, separate trendlines for males (black) and females (red) were drawn.

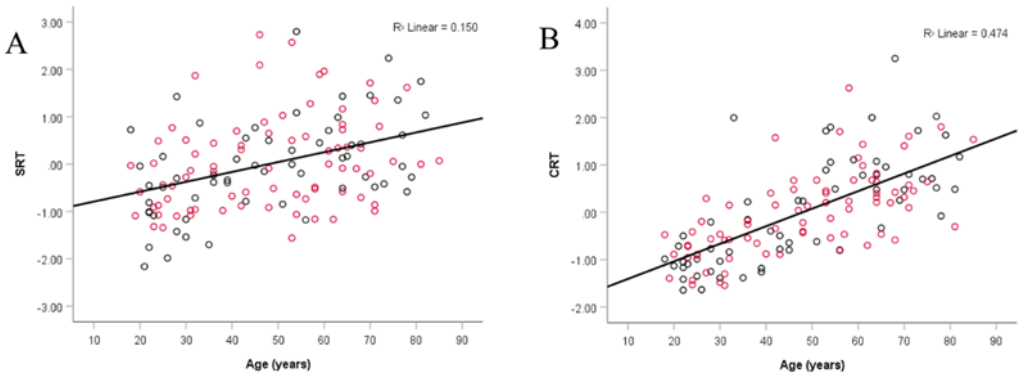

Figure 21. Simple correlation scatterplots between age and reaction times. Simple (SRT; A) and choice (CRT; B) reaction time zero order correlations with age are visualized using scatterplots.

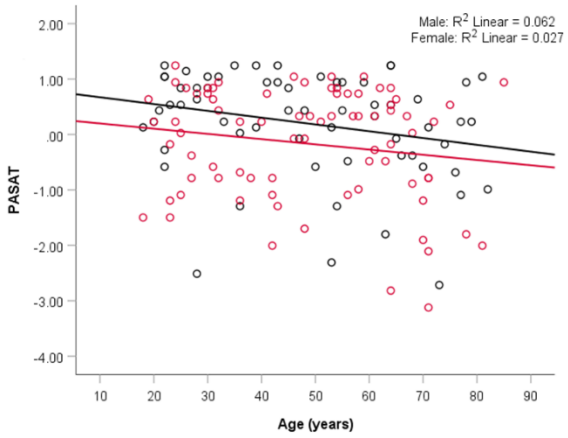

Figure 22. Simple correlation scatterplot between age and PASAT. PASAT is also significantly associated with sex, therefore separate trendlines for males (black) and females (red) were drawn.

TMT-NLS	CWI-I	CWI-IS	VF-LF	VF-CF	VF-CC	VF-CS	Sort-FS	Sort-SD	Sort-RD
-0.517	-0.617	-0.380	-0.035	-0.188	-0.204	-0.246	-0.447	-0.417	-0.340
3.4E-9	2E-13	2.8E-5	0.710	0.210	0.028	0.008	5.5E-7	4E-6	2.0E-4

LM1	LM2	LMR	VPA1	VPA2	VPAR	DE1	DE2	DER	SSP	SA
-0.270	-0.292	-0.311	-0.582	-0.579	-0.341	-0.718	-0.723	-0.628	-0.667	-0.663
0.002	0.001	3E-4	2.5E-13	3.5E-13	6.4E-5	3.1E-22	1.3E-22	7.36E-16	2.5E-18	4.6E-18

Table 12. Correlations between age and raw cognitive subtest scores. Pearson correlations (top number) and *p*-values (bottom) are presented for all subtests used in factor analysis.

3.8. Structural Equation Modeling: General Model

Structural equation models were generated based on theoretical considerations (Salthouse, 2011) and preliminary imaging and cognitive results (above). The superiority in SEM compared to zero-order correlations is its ability to account for covariance that exists within variables, and control for the effects of other predictors when calculating effects size. In all models, age and ICV were inputted as predictors of prefrontal FA. Due to known intercorrelations between age, sex, and ICV in our data set, all three variables were covaried with another and inputted as exogenous variables predicting the cognitive measures. Years of education was also inputted as a predictor for SRT. Prefrontal FA acts as the mediating variable in this model with FA values, predicted by demographic variables, set as a predictor of cognitive performance. As a result of increased model complexity and comprehensiveness, effects obtained from SEM may differ substantially from zero-order correlations; as shared variance is parceled out, previously assumed significant associations may become insignificant, and vice versa.

The resulting general SEM model is shown in Figure 23, which was ran twelve times, once for each cognitive factor or test variable. Polynomial modeling showed that the best equations to model DTI parameters included a power of age (Table 3), thus making the model non-linear in nature and violating the linearity assumption integral to GLM analyses. However, likelihood ratio based tests (Vuong, 1989), show that age declines in FA in all but one region can be adequately modeled with a linear model without conferring a statistical disadvantage. The test indicates whether the obtained non-linear optimal model fits the data significantly better than a linear model. Only the age-related decline in DLPFCR FA values showed significant non-linearity (Table 13), therefore caution must be exercised when interpreting mediative effects specific to this region. Since the general FA factor is a linear composite of all regions, minor deviations from linearity that occur in the DLPFCR and other tracts are further attenuated as factor analysis minimizes measurement error and other data irregularities present in individual indicators. Therefore, the resulting prefrontal FA variable will have a significant linear decline with age due to the overwhelming linear declines present in its constituent tracts. Since the relationships between age and cognitive scores were mostly linear in nature, the use of linear SEM to investigate the relationships between age, DTI parameters, and cognitive performance is reasonable.

SEM results differ from the initial reported associations found during preliminary analyses. Direct effects are summarized in Table 14. SEM also found that the general PFC FA factor had significant associations with age (β=-0.697, [-0.787, -0.604]) and ICV (β=0.192, [0.003, 0.377]; R^2=0.537). In addition to minor differences in effect size among previously significant direct relationships, notable changes occurred in several pathways.

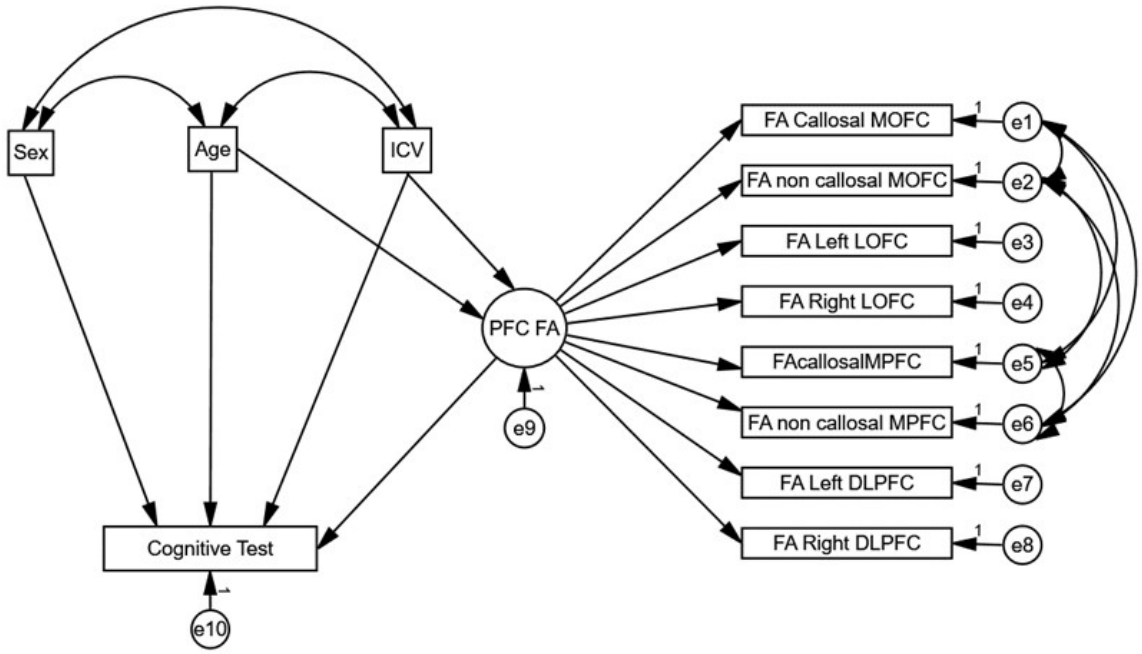

Figure 23. General causal model. The mediating effect of PFC FA on age-cognitive relationships were investigated using this structural equation model. Age, sex, and ICV are inputted as exogenous variables predicting cognitive performance alongside PFC FA which is itself predicted by age and ICV. Model was run once for each cognitive test, with the test of interest replacing the variable labeled 'Cognitive Test' in the model.

Optimal model v Linear	
Subregion FA	**Vuong LR test p-value**
MOFC callosal	0.48
MOFC Non-callosal	0.14
LOFC left	0.20
LOFC right	N/A
MPFC callosal	N/A
MPFC Non-callosal	0.10
DLPFC left	0.37
DLPFC right	0.03*

Table 13 (left). Comparison of optimal FA regression model to linear models. FA models from Table 3 were compared to models with no powers of age using a likelihood ratio (LR) test. Insignificant p-values (>0.05) mean the best fitting non-linear models were not significantly different statistically from a linear model. Tracts where the test was denoted as not applicable (N/A) are cases where the optimal model was a linear model.

Cognitive Test	Direct Pathway	Standardized Beta	Confidence interval	R^2 value
Conceptual Flexibility	Age->Conceptual Flexibility	-0.423*	[-0.654, -0.167]	0.181
	Sex->Conceptual Flexibility	0.075	[-0.126, 0.262]	
	ICV->Conceptual Flexibility	0.079	[-0.154, 0.305]	
	PFC FA-> Conceptual Flexibility	-0.016	[-0.290, 0.267]	
Inhibition	Age->Inhibition	-0.637*	[-0.826, -0.438]	0.394
	Sex->Inhibition	0.076	[-0.105, 0.248]	
	ICV->Inhibition	0.091	[-0.179, 0.333]	
	PFC FA-> Inhibition	-0.033	[-0.274, 0.223]	
Verbal Switch	Age->Verbal Switch	-0.220	[-0.491, 0.100]	0.096
	Sex->Verbal Switch	0.258*	[0.03, 0.492]	
	ICV->Verbal Switch	0.065	[-0.142, 0.282]	
	PFC FA-> Verbal Switch	0.010	[-0.309, 0.354]	
Verbal Fluency	Age->Verbal Fluency	-0.285*	[-0.513, -0.004]	0.066
	Sex->Verbal Fluency	0.170	[0.081, 0.413]	
	ICV->Verbal Fluency	0.027	[-0.214, 0.270]	
	PFC FA-> Verbal Fluency	-0.146	[-0.441, 0.183]	
Visuospatial Memory	Age->Visuospatial Memory	-0.836*	[-0.964, -0.716]	0.631
	Sex->Visuospatial Memory	0.170*	[0.039, 0.310]	
	ICV->Visuospatial Memory	0.141*	[0.014, 0.269]	
	PFC FA-> Visuospatial Memory	-0.090	[-0.261, 0.063]	
Logical Memory	Age->Logical Memory	-0.291*	[-0.521, -0.038]	0.154
	Sex->Logical Memory	0.303*	[0.094, 0.522]	
	ICV->Logical Memory	0.213*	[0.015, 0.427]	
	PFC FA-> Logical Memory	0.027	[-0.219, 0.284]	
Verbal Memory	Age->Verbal Memory	-0.790*	[-0.894, -0.528]	0.126
	Sex->Verbal Memory	0.058	[-0.121, 0.231]	
	ICV->Verbal Memory	0.031	[-0.144, 0.208]	
	PFC FA-> Verbal Memory	-0.099	[-0.308, 0.120]	
SRT	Age->SRT	0.425*	[0.197, 0.647]	0.195
	Sex->SRT	0.060	[-0.133, 0.244]	
	ICV->SRT	0.075	[-0.120, 0.283]	
	PFC FA-> SRT	0.063	[-0.202, 0.305]	
	Years of Education->SRT	-0.223	[-0.365, -0.072]	
CRT	Age->CRT	0.672*	[0.520, 0.821]	0.476
	Sex->CRT	-0.002	[-0.163, 0.165]	
	ICV->CRT	0.031	[-0.148, 0.212]	
	PFC FA-> CRT	-0.028	[-0.215, 0.168]	
PASAT	Age->PASAT	-0.067	[-0.294, 0.161]	0.108
	Sex->PASAT	-0.047	[-0.267, 0.167]	
	ICV->PASAT	0.184	[-0.096, 0.438]	
	PFC FA-> PASAT	0.157	[-0.099, 0.389]	
RMET	Age->RMET	-0.092	[-0.344, 0.180]	0.058
	Sex->RMET	0.256*	[0.039, 0.459]	
	ICV->RMET	0.156	[-0.063, 0.383]	
	PFC FA-> RMET	0.053	[-0.245, 0.353]	

Table 14. General causal model direct effects on each cognitive test. Direct effects differ from zero-order correlations due to factoring in exogenous variable covariance and directional relationships with PFC FA. *Betas marked with an asterisk are effects whose 95% percentile bootstrapped confidence intervals did not contain zero are considered significant.

Verbal Switch no longer significantly declines with age after controlling for covariates (β=-0.220, [-0.491, 0.100]), but retains its sex difference (β=0.258, [0.03, 0.492]); while Verbal Fluency, which previously was not associated with age, develops a significant negative association after covariate consideration (β=-0.285, [-0.513, -0.004]). All three WMS-IV factors retained their significant direct relationships with age, with Logical Memory and Visuospatial Memory gaining significant associations with sex (β=0.303, [0.094, 0.522] and β=0.170, [0.039, 0.310]) and ICV (β=0.213, [0.015, 0.427] and β=0.141, [0.014, 0.269]), with higher scores in females and with greater ICV values. PASAT results obtained through SEM greatly differ from their zero order correlations, with all previous age (β=-0.067, [-0.294, 0.161]), sex (β=-0.047, [-0.267, 0.167]), and ICV (β=0.184, [-0.096, 0.438]) direct effects becoming insignificant. SEM also uncovered a sex effect in RMET scores, with higher average scores in women compared to men (β=0.256, [0.039, 0.459]). Prefrontal FA, which was also assigned to predict cognitive scores, was not found to produce a direct effect on any of the cognitive scores (Table 14). As a result, the general FA model did not find any significant indirect effects of age or ICV with prefrontal FA acting as a mediator (Table 15) for any cognitive test studied.

Cognitive Test	Indirect Pathway	Standardized Beta	Confidence interval
Conceptual Flexibility	Age->Conceptual Flexibility	0.011	[-0.202, 0.202]
	ICV->Conceptual Flexibility	-0.003	[-0.061, 0.045]
Inhibition	Age->Inhibition	0.023	[-0.165, 0.201]
	ICV->Inhibition	-0.005	[-0.050, 0.042]
Verbal Switch	Age->Verbal Switch	-0.007	[-0.263, 0.219]
	ICV->Verbal Switch	0.002	[-0.063, 0.066]
Verbal Fluency	Age->Verbal Fluency	0.104	[-0.136, 0.315]
	ICV->Verbal Fluency	-0.024	[-0.096, 0.028]
Visuospatial Memory	Age->Visuospatial Memory	0.064	[-0.045, 0.194]
	ICV->Visuospatial Memory	-0.014	[-0.051, 0.009]
Logical Memory	Age->Logical Memory	-0.02	[-0.207, 0.157]
	ICV->Logical Memory	0.004	[-0.039, 0.052]
Verbal Memory	Age->Verbal Memory	0.071	[-0.089, 0.223]
	ICV-> Verbal Memory	-0.016	[-0.063, 0.018]
SRT	Age->SRT	-0.045	[-0.222, 0.147]
	ICV->SRT	0.008	[-0.03, 0.045]
CRT	Age->CRT	0.020	[-0.124, 0.160]
	ICV->CRT	-0.003	[-0.037, 0.022]
PASAT	Age->PASAT	-0.110	[-0.279, 0.072]
	ICV->PASAT	0.022	[-0.014, 0.074]
RMET	Age->RMET	-0.037	[-0.254, 0.173]
	ICV->RMET	0.007	[-0.043, 0.055]

Table 15. General causal model indirect effects on each cognitive test. The mediating effect of PFC FA, for both age and ICV, on all cognitive tests is present alongside its 95% percentile bootstrapped confidence interval. No indirect effect was found to be significant.

3.9. Structural Equation Modeling: Single Tract Mediation

SEM models testing the effects of specific subregion FA values were generated by replacing the global PFC FA latent factor in the previous model with each tract specific FA value for each test (Figure 24). Since the models do not portray a classic 3-variable mediation model, the models are not saturated, and we cannot assume perfect model fit. However, due to their relative parsimony, all single tract mediation models achieved excellent model fit based on our fit statistic criteria.

The direct effects of age, sex, ICV, and tract FA on each cognitive test were measured in addition to 2 indirect effects of age and ICV on cognitive test scores, as mediated by tract FA. A total of 10 significant indirect effects were recorded, summarized in Table 17.

FA values in the left LOFC mediated the most effects, with direct effects on Conceptual Flexibility (β=-0.217, [-0.386, -0.042]), Visuospatial Memory (β=-0.122, [-0.239, -0.006]), and SRT scores (β=0.190, [0.027, 0.345]).

These direct effects produced significant age and ICV indirect effects in Conceptual Flexibility (β=0.104, [0.02, 0.199]; β=-0.034, [-0.083, 0.000]), Visuospatial Memory (β=0.053, [0.002, 0.113]; β=-0.022, [-0.057, 0.000]), and SRT (β=-0.083, [-0.169, -0.021]; β=0.03, [0.003, 0.084]). In each case, the direction of the effect is positive in age and negative in ICV.

FA values in the right LOFC also mediated Visuospatial Memory but the signage was inverted, the direct effect of right LOFC FA was positive (β=0.143, [0.03, 0.261]), producing indirect effects where increased age and lower ICV resulted in lower VS scores (β=-0.051, [-0.109, -0.009]; β=0.025, [0.000, 0.066]).

Callosal MOFC FA had significant direct effects on CRT (β=-0.154, [-0.291, -0.016]) and RMET (β=0.210, [0.022, 0.382]) scores. These produced significant indirect effects of age on CRT through callosal MOFC FA in CRT (β=0.081, [0.008, 0.166]), and although age has no effect on RMET values, increased age is associated with decreased RMET scores through its relationship with callosal MOFC FA (β=-0.110, [-0.203, -0.012]).

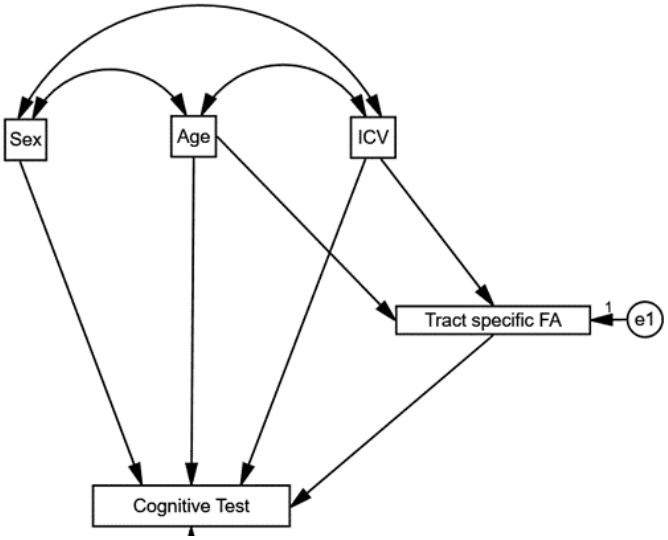

Figure 24. Single tract causal model. The mediating effect of specific subregion FA on age-cognitive relationships were investigated using this structural equation model. Age, sex, and ICV are inputted as exogenous variables predicting cognitive performance alongside PFC FA which is itself predicted by age and ICV. Model was run once for each tract and cognitive test combination, with the test of interest replacing the variable labeled 'Cognitive Test' in the model, and each subregion FA replacing 'Tract specific FA'.

Cognitive Test	Direct Pathway	Standardized Beta	Confidence interval
Conceptual Flexibility	LOFC Left->Conceptual Flexibility	-0.217	[-0.386, -0.042]
Visuospatial Memory	LOFC Left->Visuospatial Memory	-0.122	[-0.239, -0.006]
	LOFC Right->Visuospatial Memory	0.143	[0.03, 0.261]
SRT	LOFC Left->SRT	0.190	[0.027, 0.345]
CRT	MOFC callosal->CRT	-0.154	[-0.291, -0.016]
RMET	MOFC callosal->RMET	0.210,	[0.022, 0.382]

Table 16. Single tract causal model direct effects of FA values on cognitive scores. After account for the effects of age, ICV, and sex, FA values of specific tracts have significant direct effects on various cognitive scores. The standardized direct effect alongside its 95% percentile bootstrapped confidence interval is presented.

Cognitive Test	Indirect Pathway	Standardized Beta	Confidence interval
Conceptual Flexibility	Age->LOFC Left->Conceptual Flexibility	0.104	[0.02, 0.199]
	ICV->LOFC Left->Conceptual Flexibility	-0.034	[-0.083, 0.000]
Visuospatial Memory	Age->LOFC Left->Visuospatial Memory	0.053	[0.002, 0.113]
	ICV->LOFC Left->Visuospatial Memory	-0.022	[-0.057, 0.000]
	Age->LOFC Right->Visuospatial Memory	-0.051	[-0.109, -0.009]
	ICV->LOFC Right->Visuospatial Memory	0.025	[0.000, 0.066]
SRT	Age->LOFC Left->SRT	-0.083	[-0.169, -0.021]
	ICV->LOFC Left->SRT	0.03	[0.003, 0.084]
CRT	Age->MOFC callosal->CRT	0.081	[0.008, 0.166]
RMET	Age->MOFC callosal->RMET	-0.110	[-0.203, -0.012]

Table 17. Single tract causal model indirect effects on each cognitive test. Pathways with significant mediating effects from tract FA values are presented in the second column. The standardized indirect effect alongside its 95% percentile bootstrapped confidence interval is presented, all shown effects are significant.

4. Discussion

The study investigated the effects of age on WM integrity contained within specific prefrontal subregions and whether age differences in integrity mediated the age-related decline in cognitive performance. Relationships between age and DTI parameters were first modelled using higher order polynomial regression modelling and found that most parameters displayed non-linear effects of age. The effects of age were not uniform across all subregions, which experienced varying rates of decline, the callosal MPFC was among the most affected by age while the LOFC was least affected. Despite significant effects of age on both WM integrity and cognitive performance, FA values were largely not related to cognitive performance. However, orbitofrontal FA was found to partially mediate the effects of age on performance on certain cognitive tasks.

4.01. Higher Order Modeling of DTI Parameters

The first goal of the study was to use DTI-tractography to investigate the effects of aging on white matter connections within specific prefrontal subregions. An advantage of our study was the employment of higher order polynomial regression models to visualize the trajectories of age effects, as done previously to callosal WM tracts (Pietrasik *et al.*, 2020). Our HO modelling uses BIC to select which powers of age, alongside potential demographic covariates such as sex and ICV, best model the relationship between age and DTI parameters. HO polynomial regression allows us to investigate the trajectory of these age-parameter relationships in greater detail, and better visualize their complexity and non-linearity (Fjell *et al.*, 2010; Ostertagová, 2012; Ziegler *et al.*, 2012). In addition to the more commonly studied DTI measures such as FA, RD, MD, and AD, we also modeled age effects on prefrontal fiber counts, fiber lengths, fiber volumes, and fibers per voxel for the first time with the goal to further understand the effects of age on both prefrontal micro and macrostructure. The inclusion of potential demographic variables (sex and ICV) were incorporated to provide further clarification of their impact on the studied variables.

HO polynomial regression modeling showed that most associations between age and DTI parameters in prefrontal tracts are non-linear in shape. A total of 64 regressions were obtained across all tracts and parameters, of which 56 were best fit with a non-linear model. Of these 56, 35

include higher order powers of age (base 4 and above), while the remainder follow quadratic, cubic, or linear trajectories.

Non-linear effects of age on WM have been extensively reported (Allen *et al.*, 2005; Raz *et al.*, 2005; Westlye *et al.*, 2010; Kochunov *et al.*, 2012), particularly in anterior WM (Michielse *et al.*, 2010; Lebel *et al.*, 2012); however, past studies were limited to quadratic and cubic terms in measuring non-linearity. While HO modeling allows for better description of non-linear patterns, the application of HO modeling to visualize trajectories of WM aging is not common. In our previous study employing HO modeling for the corpus callosum (Pietrasik *et al.*, 2020), we found that all significant age effects on DTI parameters were non-linear, with most effects fit best by a higher power of age. Strong effects of age, such as those in the genu, did not require HO models to visualize parameter relationships with age while weaker effects in the splenium included HO powers in their best fit models. Similarly, in the current study, while the strongest effects, and those with earliest onsets, may not include HO powers of age, the weaker effects in AD or volume (Tables 6 and 8) chose HO powers in their best fit models. These HO powers were necessary to describe and visualize age effects with very late onsets (Figures 11 and 13).

Therefore, using HO models is useful when measuring subtler age effects that would otherwise be missed entirely or labeled as insignificant if only linear or LO models were available. Applying HO modeling to the present study allowed us to examine WM differences that occur only in advanced age.

4.02. Effects of Age on Prefrontal Microstructure

Microstructural properties of the prefrontal tracts were assessed using the FA, MD, AD, and RD parameters extracted from DTI. Although these measures reflect properties of water diffusion within millimeter sized voxels and not the cellular level, they are used to infer microstructural properties, with each parameter ascribed to specific phenomena.

All prefrontal tracts displayed age effects in FA, AD, RD, and MD, with FA decreases and diffusivity increases occurring with increased age. Across all prefrontal subregions the DTI parameters consistently found to be most affected by age were FA and RD. Although substantial

variation occurred across tracts, FA and RD models had the highest R^2 values, indicating the strongest effects of age, or age and covariates, for these parameters.

Age-related FA declines were most prominent in the MOFCnc, MPFCc, and DLPFCR, with the weakest effects in the LOFC. FA models notably did not include any HO powers of age; quadratic fits were dominant and the relationships in the LOFCR and MPFCc were best described as linear. Consequently, FA values did not exhibit relative stability during adulthood, with the onset of FA decline occurring between 20 and 30 years of age (Figure 8). Indeed, although the best fitting models, and those that explained the most age-related variance, were non-linear, LR tests showed no statistical differences between non-linear and linear models for FA in all but one subregion (Table 13); this suggests that FA declines could be described as progressing in a linear fashion. A linear declines in FA with age, even when non-linear models were considered, has been found to occur both in global FA (Hsu *et al.*, 2010; Westlye *et al.*, 2010) and prefrontal WM (Bartzokis *et al.*, 2012).

In contrast to FA, age effects on diffusivity terms, such as MD, AD, and RD, showed more pronounced non-linearity. Diffusivity terms typically experienced greater stability with increased age, with rapid exponential increases occurring between 50 and 60 years of age.

Like FA, the effects of age on RD were most prominent in the MOFCnc, DLPFCR, and MPFC tracts, and weakest in the LOFC (Table 5). The exponential rise in RD occurred around 50 years of age, although increases did occur prior to 50, particularly in the MOFCc (Figure 10). This extended period of relative stability in adulthood followed by a rapid increase resulted in significant non-linearity in RD models, with all subregions selecting quadratic, cubic, or quartic powers of age. Compared to RD, age-related increases in AD were much weaker. Effects of age were strongest in the DLPFC tracts and marginal in the MPFCnc, with R^2 values ranging between 0.1 and 0.2. Age effects in AD were exceptionally non-linear, with HO models chosen in most cases. This is reflected in the trajectories of AD increase (Figure 11), which often showed AD increases as occurring very late in life after prolonged periods of stability. The contrast between RD and AD demonstrates a link between the strength and stability of the relationship and the power of age chosen. The strong effects in RD select LO or quartic (4^{th} power) HO models while AD is modeled predominantly by higher powers of age. Higher powers of age are necessary to confirm the presence of a significant relationship that would otherwise not be observed using LO or linear

modeling. To model the minor effect of age on AD in the MPFCnc, in which AD increases occurred only after 70 years of age, a decic power was required. Meanwhile, the strongest relationships that showed earlier inflections and less middle age stability, such as AD in the MOFCc, chose a LO quadratic power of age. Lastly, MD, being a composite measure of RD and AD, had effect sizes lower than RD and higher than AD; similarly, the powers of age chosen in the best fitting model were largely in-between those found in RD and AD.

The age effects observed on prefrontal microstructure are mostly consistent with previous findings. While many studies limit anterior or frontal projecting WM to the rostral cingulum or genu of the corpus callosum (Michielse *et al.*, 2010; Sullivan *et al.*, 2010b; Lebel *et al.*, 2012), several studies have investigated the effects of age on non-callosal prefrontal WM. The earliest studies investigating prefrontal WM not within the CC found a decline in FA values, specifically in the orbitofrontal and ventromedial regions (Raz *et al.*, 2004; Raz *et al.*, 2005; Salat *et al.*, 2005). Bartzokis and colleagues compared age-related effects on WM in prefrontal areas, the genu, and the splenium. They found that the late-myelinating frontal and genu WM was more vulnerable to aging than the posterior splenium, with more pronounced decreases in FA and increases in RD (Bartzokis *et al.*, 2012). In addition, prefrontal WM was significantly more affected by age than the genu, in agreement with previous patterns (Burgmans *et al.*, 2010), thus demonstrating the need to measure non callosal prefrontal WM as a distinct entity. Our lab (Malykhin *et al.*, 2011) has previously used DTI to investigate the effects of aging on the prefrontal subregions segmented in this study. Results from polynomial regression modeling are broadly in alignment with our previous work, as both studies showed all prefrontal subregions were affected by age, with declines in FA and increases in all diffusivity measures. Non-linear relationships were found in most parameters, diffusivity values remained relatively stable until around 60 years of age where exponential increases occurred, similar to present findings. While both studies produced similar effect sizes for FA in the MOFC and DLPFC tracts, especially noting the vulnerability of the MOFCnc to age, the present study found strong effects in the MPFC and weak effects in the LOFC while the past study found weaker effects in the MPFC and stronger effects in the LOFC. However, Malykhin *et al.* was subject to several limitations, lateral tracts were not split by hemisphere, sex and ICV were not included as covariates, and the study sample lacked participants between 60 and 70 years of age. These differences may have contributed to slightly divergent results.

In summary, despite considerable diversity in tractography methods and segmentation protocols across studies, strong effects of age on prefrontal WM microstructure are consistently observed. Our study extended these findings by measuring distinct prefrontal subregions using HO modeling, discovering that significant non-linear age-effects are widespread across the entire PFC.

4.03. Effects of Sex and ICV on Prefrontal Microstructure

In addition to powers of age, several models selected sex or ICV as a significant predictor of microstructural parameter differences in our sample. Although diffusivity values were not found to be influenced by sex, ICV, or any interaction terms, FA models in several prefrontal subregions included additional variables to achieve superior fit.

ICV predicted FA values in the LOFC tracts, with greater ICV associated with greater FA values. This finding is in line with previous studies that showed a similar ICV-FA relationships in various WM tracts (Takao *et al.*, 2011; Takao *et al.*, 2013). A significant sex difference was present in the MOFCnc, with larger FA values in males on average. Although no study has previously investigated sex differences on this specific tract, higher FA values in men have been reported in various tracts (Chou *et al.*, 2011; Inano *et al.*, 2011; Menzler *et al.*, 2011), including frontal WM (Sullivan *et al.*, 2010b); although opposite patterns have been noted, such as higher FA values in the left frontal lobe in women (Szeszko *et al.*, 2003). The singular sex effect found in this study adds to the abundance of inconclusive findings of WM sex differences that fail to demonstrate consistent patterns or a convincing etiology. The remaining interaction terms are largely explained by the significant age*sex*ICV interaction found in our sample population where increased age is associated with lower ICV values in men but not women. This interaction may be due to the sample composition or be a result of increases in mean weight and height in the last 40 years in both males and females (Ogden *et al.*, 2004; Nguyen *et al.*, 2012). The ICV*sex association in the MOFCnc is a consequence of this interaction, older males have lower ICV values, leading to lower FA. This is also the case for the ICV*sex*age interaction in the right DLPFC. Finally, the significant age*sex interaction in the right DLPFC reflects an accelerated age-related decline in the right DLPFC for women. This finding appears novel, as previous studies found no sex differences in

WM aging rates (Kodiweera *et al.*, 2016), or found that men show faster rates of decline in prefrontal WM (Raz *et al.*, 2004).

Models that included ICV, or an ICV containing interaction term, produced non-smooth trendlines on scatterplots, are an inherent consequence of the impact of individual ICV. As observed in our previous study (Pietrasik *et al.,* 2020) ICV in males, but not females, declines with age. Younger participants will therefore have inflated FA values and older participants will have lower FA values which leads to the characteristic trendline inflections at the tail ends of the curves.

4.04 Interpretation of Effects on Microstructure

The microstructural parameters obtained with DTI measure unique properties of intravoxel water diffusion. By measuring, and interpreting, all parameters, we may obtain additional information about the local microstructure and speculate on the mechanisms behind age-related differences in WM integrity. The primary DTI measure, FA, describes the shape and principal direction of water diffusion (Pierpaoli & Basser, 1996) which may reflect fiber coherence and density within a voxel (Beaulieu, 2002; Beaulieu, 2014) and provide a general measure of WM integrity. AD and RD are more specific measures relating to the parallel and perpendicular components of the diffusion tensor, respectively. These parameters have been linked to unique etiologies, with increases in AD believed to indicate axonal injury and degeneration (Song *et al.*, 2003; Sun *et al.*, 2006; van de Looij *et al.*, 2012; Wang *et al.*, 2012), while changes in RD have been linked to myelin levels and demyelination (Song *et al.*, 2002; Nair *et al.*, 2005; Song *et al.*, 2005), although caution should be exercised at implying direct causal links (Budde *et al.*, 2007; Wheeler-Kingshott & Cercignani, 2009). Increases in MD result from either increases in AD, RD, or both, and generally reflect extracellular alterations leading to increased extra axonal fluid (Sen & Basser, 2005).

Our study supports previous literature that found FA and RD to be the DTI parameters most affected by age, with weaker, but significant, effects in AD (Davis *et al.*, 2009; Bennett *et al.*, 2010; Zhang *et al.*, 2010). The strong emphasis on RD suggests that the decline in WM integrity, as measured by FA, may be primarily driven by age-related demyelination. While intravoxel decreases in FA with concurrent increases in RD are the most common pattern observed in aging WM across the brain (Bennett *et al.*, 2010; Burzynska *et al.*, 2010), prefrontal tracts also showed

AD increases with age. Patterns displaying a decrease in FA with increases in all diffusivity metrics are also frequently encountered (Sexton *et al.*, 2014). Burzynska and colleagues found this pattern was prevalent across many WM tracts, including the genu of the corpus callosum and WM within the dorsal middle frontal gyrus. The authors attributed this pattern to chronic WM degeneration found with advanced age, and in cases of chronic WM damage, characterized by degeneration of both axonal membranes and myelin sheaths leading to increases in extracellular volume (Burzynska *et al.*, 2010). A more recent study also found the most common pattern of age effects involved primarily decreases in FA with increases in RD, which occurred in nearly a third of the voxels measured (Molloy *et al.*, 2021). Interestingly, the study found very few voxels which exhibited AD increases with age, limited to the genu and anterior thalamic radiations, with more voxels experiencing AD decreases with age. This may, however, further reflect the limitation of using linear models to characterize age-effects in parameters known to deviate far from linearity, as seen in the late-age effects on AD in our study.

In addition to age, ICV was also selected as a significant predictor of FA, but not AD or RD values, with greater ICV linked to higher FA. This relationship may be due to partial volume effects and microarchitectural differences due to ICV differences. Brain structures scale with head size; larger ICV values are associated with larger fiber bundles and can alter bundle thickness, orientation, and curvature, which affects fiber coherence and FA (Vos *et al.*, 2011). With a greater number of voxels, larger brains have 'relatively' smaller voxels than smaller brains; smaller voxels experience less partial volume effects and are less likely to contain crossing fibers, leading to higher FA values (Alexander *et al.*, 2001; Oouchi *et al.*, 2007). LOFC tracts are small, have the lowest baseline FA values, and show the weakest effects due to age compared to other tracts; they may be particularly vulnerable to crossing fiber effects that are partly attenuated by greater ICV.

In summary, the observed effects of age on prefrontal WM microstructure are consistent with previous studies, and suggest aging is characterized primarily by demyelination, and to a lesser extent, axonal degeneration. However, inferring true WM integrity from DTI parameters remains challenging. FA is not a pure microstructural measure, it is influenced by ICV, crossing fibers, and broader tract organization (Jeurissen *et al.*, 2013; Billiet *et al.*, 2015) which prevents us from reducing the effects of aging into a single mechanism.

4.05. Effects on Prefrontal Macrostructure

Compared to microstructural measures, parameters relating to broader tract organization, such as, fiber count, average fiber length, tract volume, and average fibers per voxel, tended to have weaker and more irregular relationships with age (Tables 7-10). As with microstructural parameters, the weakest effects often included HO powers of age in their best fitting model, which are necessary for visualizing the exceptionally non-linear decline that occurs only at the oldest ages. Macrostructural measures also generally included ICV as an additional predictive variable in their models, with the exception of tract volumes which were ICV adjusted, with greater ICV predicting more, longer, and more densely packed fibers. Estimating true effects of age in microstructural parameters is difficult as the model R^2 is not solely reflective of the predictive capabilities of age. Therefore, the interpretation of model R^2 values as strictly age predicted variance is true only in cases where no additional predictors were selected, such as tract volumes.

The macrostructural measure with the highest R^2 was fiber count. Apart from the MOFCc, which showed a marginal effect of age, fiber counts had moderate non-linear decreases with age in all other prefrontal subregions (Figure 12). Inclusion of ICV as an additional parameter in the model produced noticeable drops in fiber count trendlines that occurred between 20 and 30 years of age and after 70 due to disproportionately low ICV values in the oldest males in our sample. As a result, calculating the onset of decline in macrostructural measures proves difficult when ICV is included as a predictor. Models describing differences in average fiber length were inconsistent across prefrontal subregions. Both callosal and non-callosal MPFC tracts exhibited a moderate decline in length with age while the remaining prefrontal subregions were less affected. In the LOFCR and DLPFCL, the effects of age were insignificant, however other parameters such as ICV were selected as significant predictors of length, therefore a significant model was still generated. The DLPFCL was a particularly unique case where a significant effect of age was found, but only in women, while the age variable remained insignificant when considering the entire sample. Like fiber count, fiber length models showed a non-linear decline with age, with similar ICV-related drops at the tail ends of the regression (Figure 14); however, the weakness of the age-effects are highlighted by the extended period of stability in middle age.

Tract volumes exhibited weak relationships with age, with the strongest effect in the MPFCc. Similar to fiber length, the weak associations reflect age effects that occurred at advanced ages

with decline onsets occurring around 60 (Figure 13); these weaker effects require HO models to be visualized. Average fibers per voxel showed great inconsistency in its age effects. No effects of age were observed in the MPFCnc and left DLPFC, which was instead predicted mainly by ICV. Where significant, the age-related decline was mostly non-linear, although linear declines were found in the left LOFC and the MOFCc, with the latter being marginally significant. As with the other macrostructural parameters, effects were strongest in the MPFCc, followed by the right DLPFC and the right LOFC. The left DLPFC, although not predicted by age, nonetheless had a R^2 value comparable to its age affected right counterpart, suggesting that a significant portion of the interindividual variance in fibers per voxel is explained by ICV, with age, where applicable, serving as a less prominent predictor.

Across all macrostructural parameters, the MOFCc, the smallest tract measured, had the lowest R^2 values. ICV was not included as a predictor for any macrostructural measure in the MOFCc, which suggests that ICV may predict a substantial amount of variance in fiber counts. As with microstructural measures, WM within the LOFC was poorly modeled by age and ICV in macrostructural properties, followed by the DLPFC. The MPFCc appeared the most strongly affected by age in their macrostructure, with the greatest decreases in fiber count, length, volume, and fibers per voxel with age. The MPFCnc, while still showing a decline in fiber count and length, was less affected in volume and not affected in fibers per voxel. The non-linear declines in prefrontal WM volumes are consistent with previous literature reporting global (Jernigan *et al.*, 2001; Giorgio *et al.*, 2010; Walhovd *et al.*, 2011), as well as frontal (Bartzokis *et al.*, 2001; Bartzokis *et al.*, 2003; Salat *et al.*, 2009; Malykhin *et al.*, 2011) non-linear declines in WM volumes, including WM within the subregions defined in this study. Apart from tract volume, macrostructural parameters are seldom reported in DTI studies. Unlike microstructural measures of AD and RD, which are theoretically orthogonal, macrostructural measures are highly interdependent; all macrostructural parameters are also heavily influenced by ICV, limiting the measurement of non-redundant variance, and complicating the analysis of age-effects. In addition, confounding factors make interpretation difficult, fiber counts and fibers per voxel are not true measures of axons number and axon density and are heavily influenced by fiber curvature, width, length, and myelination (Jones *et al.*, 2013). The decline in the number and length of fibers with age have, instead, been confirmed mostly by postmortem autopsy studies. Several studies (Tang *et al.*, 1997; Peters, 2002; Marner *et al.*, 2003) have found fewer and shorter WM fibers in the

brains of deceased elderly compared to young adults, with degeneration particularly affecting smaller diameter axons prevalent in frontal regions. These postmortem findings have been corroborated by the few in vivo DTI studies that measured macrostructural parameters and reported both decreased fiber counts and fiber lengths in frontal WM with advanced age (Gao *et al.*, 2011; Behrman-Lay *et al.*, 2015). The decrease in values measuring macrostructural properties of prefrontal WM are now further corroborated by our study, which is the first to examine age effects in prefrontal subregions. The results demonstrate that MPFCc WM macrostructure is disproportionately vulnerable to age-related decline while WM within the smaller LOFC and MOFC shows greater preservation with age.

4.06. Prefrontal Patterns of Aging

Although substantial variation occurs among tracts and parameters, several patterns emerge regarding the vulnerability of specific prefrontal subregions to aging. Overall, the effects seen in FA are exemplary of the effects seen in all parameters, both microstructural and macrostructural. MPFCc WM is most affected by age, consistently producing strong age-effects across parameters; WM within the DLPFCR, MOFCnc, and MPFCnc follow. The remaining OFC tracts, the LOFC in particular, are least affected by age. Both the right and left LOFC consistently show the weakest effects due to age.

Subregional differences can also be characterized based on specific neuroanatomical contrasts. When comparing callosal and non-callosal tracts, the MOFCc tends to have weaker age effects than the MOFCnc in both microstructural and macrostructural parameters, although effects of age on macrostructure are relatively minor for OFC tracts in general. However, this pattern is inconsistent with the MPFC where microstructural measures are similar in callosal and non-callosal tracts, but the callosal MPFC is more affected in macrostructural measures compared to the non-callosal MPFC.

An examination of hemispheric effects among the lateral tracts shows that the left and right LOFC are similar in both micro and macrostructural parameters, while the DLPFCR seems to be more affected than the DLPFCL in microstructural measures but remains similar to the DLPFCL in macrostructural measures.

Comparing medial tracts (MOFC, MPFC) and lateral tracts (LOFC, DLPFC) finds minor differences. The LOFC tracts, due to having the weakest age-effects of all subregions, are comparatively less affected by aging than the MOFC tracts. This pattern does not persist in the superior tracts between the MPFC and DLPFC.

Lastly, a comparison between superior (MPFC, DLPFC) and inferior (MOFC, LOFC) tracts showed that, similar to the medial-lateral contrast, the weak effects in the inferior LOFC produce a noticeable contrast to the superior DLPFC. The superior tracts, MPFC in particular, are decidedly more affected in their macrostructural measures, where larger tracts are more affected than smaller tracts. Differences in microstructural parameters due to age are fairly comparable between the MOFC and MPFC.

When comparing age-effects on WM across the brain, past studies focused primarily on the differing rates of decline found between anterior and posterior WM (Davis *et al.*, 2009; Michielse *et al.*, 2010; Bartzokis *et al.*, 2012). Whether the rate of WM decline also follows preferential directionality on the superior-inferior or medial-lateral axis has been less well investigated. A superior-inferior effect, where superior tracts experience greater WM decline, has been reported before (Zahr *et al.*, 2009; Sullivan *et al.*, 2010b; Sexton *et al.*, 2014), and is consistent with findings in GM (Zimmerman *et al.*, 2006). Superior fibers were found to have disproportionately lower FA and greater RD with age compared to inferior tracts, suggestive of a myelin compromise. However, this contrast was found primarily in association fibers such as the cingulum, uncinate fasciculus, superior and inferior longitudinal fasciculi, as well as the genu. The existence of a medial-lateral directionality is not well reported, limited mostly to the corpus callosum. Sullivan and colleagues divided callosal fibers into midsagittal and distal, and observed lower mean FA in the distal regions, in accordance with our findings (Sullivan *et al.*, 2010a). A stronger effect of age on distal fibers compared to midsagittal was also found; however, this was limited to postcentral callosal fibers and not those contained within the frontal lobe. Lebel *et al.* ran a similar comparison in the corpus callosum (Lebel *et al.*, 2010); in addition to higher FA values in the midline CC, they found that the anterior and superior frontal callosum showed a greater decline in FA in the lateral fibers compared to medial fibers, while the orbitofrontal CC did not produce this effect. The authors concluded that the decline in callosal integrity seen with age may be primarily driven by the lateral CC than the medial CC. Our previous study examining the effects of age on the WM of these

subregions found neither a superior-inferior or medial-lateral directionality, with no large discrepancies between the effect sizes of the various tracts (Malykhin *et al.*, 2011); however, the observation of directionality in the present study may be due to the use of more sophisticated HO modelling.

In both the superior-inferior and medial-lateral effects noted in this study the primary drivers are the LOFC tracts, which display significantly weaker age-effects than all other tracts, and to a lesser extent the MPFCc which shows increased vulnerability with age. The greater vulnerability of the MPFCc is likely a result of its structural overlap to the age susceptible CC genu. These anterior callosal fibers are weakly myelinated or unmyelinated making them particularly susceptible to aging (Aboitiz *et al.*, 1992; Marner *et al.*, 2003; Callaghan *et al.*, 2014). The weaker effects of age observed in the LOFC may lend further evidence to the "last in, first out" hypothesis of the frontal theory of aging, in which WM which myelinates latest is the first to show an age-related decline in integrity. While all prefrontal regions myelinate late compared to posterior areas, the medial MOFC and MPFC myelinate later than the LOFC and DLPFC (see Fuster, 2002).

Myeloarchitectonic studies of the PFC have provided mixed results. Ongur *et al.* showed that the agranular insula and Brodmann areas corresponding to the LOFC (47/12s) have very sparse myelination (Ongur *et al.*, 2003), which should make it more susceptible to aging than medial regions. However, which architectonic regions make up the LOFC varies (Price, 2007; Uylings *et al.*, 2010), and the LOFC region delineated in our study may be contaminated by fibers in adjacent areas 47/12l and 47/12m which are heavily myelinated. Other studies with slightly different parcellation of prefrontal areas have shown opposite trends with a greater density of myelinated fibers present in the LOFC compared to the MOFC and MPFC (Nieuwenhuys & Broere, 2017). It should be noted that the prefrontal gyri and sulci used to delineate PFC regions were not used as the sole anatomical landmarks during subregion segmentation in this study as cortical areas delineated using conventional MRI do not provide information about the organization of the underlying white matter. In consideration of these anatomical uncertainties, further studies using reliable and consistent segmentation protocols, designed to specifically delineate WM within particular gyri, are required to determine whether the resistance of LOFC WM to aging is a persistent pattern.

4.07. Superficial White Matter

WM within the frontal lobes has rarely been segmented into prefrontal subregions to allow for specific analysis of age-effects on localized WM. Proper comparison with other studies is limited, although few studies utilized ROI-based methods to study prefrontal subregion WM (Kennedy & Raz, 2009; Malykhin *et al.*, 2011; Bartzokis *et al.*, 2012), recent interest in superficial WM (SWM), which includes intracortical axons and short U-shaped fibers connecting neighboring gyri (Guevara *et al.*, 2020), have investigated the effects of age on SWM in prefrontal regions. SWM, and not long WM tracts, comprise the majority of WM in the brain (Schüz & Braitenberg, 2002; Paus *et al.*, 2014); the small ROIs in this study were specifically designed to capture SWM connections limited to the PFC.

SWM may be more susceptible to the effects of age than deep white matter, SWM myelinates late in development (Kinney *et al.*, 1988; Parazzini *et al.*, 2002), much like the most age vulnerable WM. SWM is less densely myelinated, less coherent, and contains more crossing fibers, leading to complex trajectories and lower FA (Oishi *et al.*, 2008; Wu *et al.*, 2014). These effects may be further amplified in frontal SWM, as frontal SWM contains less interstitial neurons than SWM in other lobes (Defelipe *et al.*, 2010); these neurons are important in guiding axons during development, and a decrease in frontal interstitial neurons have been associated with neurodegenerative conditions, leading to lower FA (Suarez-Sola *et al.*, 2009).

A seminal study investigating age effects on SWM was conducted by Phillips and colleagues (Phillips *et al.*, 2013). They found that prefrontal SWM was most sensitive to age compared to posterior SWM, with the medial and dorsolateral prefrontal regions being prominently affected. The effects of age could be described as both linear and LO non-linear as both models reached significance. Declines in FA were concurrent with increases in RD and AD in the lateral prefrontal regions, while callosal and cingulate WM experienced an FA decline and RD increase without significant effects on AD. Nazeri *et al.* showed similar results, with strong linear and non-linear declines in FA occurring in prefrontal SWM with age, particularly in the MOFC and MPFC (Nazeri *et al.*, 2015). The study also found that there is a significant relationship between SWM FA and frontal surface area, demonstrating that brain size, or ICV, may influence FA values. While

these studies showed largely bilateral age-effects, Rojkova and colleagues, who generated an atlas of various frontal tracts, found the most prominent declines in FA in regions corresponding to the left LOFC and left DLPFC, in addition to the MPFCnc (Rojkova *et al.*, 2016). Non-linear age-effects were also found in the magnetization transfer ratio (MTR), a measure specific to myelin with decreases in MTR linked to demyelination (Wu *et al.*, 2016). A decline in MTR was found in SWM regions corresponding to the MPFCnc, DLPFC, and MOFC, indicating accelerating demyelination after the age of 60, with linear declines in the lateral LOFC and MPFCc.

Studies investigating frontal SWM provide substantial heterogeneity in their results, many similarities among these studies are consistent with our results. FA age-effects could be described linearly or non-linearly and were subject to the influence of ICV; in addition, superior regions were found to be more affected than inferior, MPFC WM had stronger age effects while LOFC WM was less affected. As mentioned previously, there is no unanimous agreement on anatomical delineation in the PFC. Therefore, methods and segmentation protocols are not consistent across studies. No pattern regarding subregional declines, with preferential susceptibility of specific subregions, has emerged, suggesting all prefrontal subregions show weaker WM integrity with age.

4.08. Evaluation of Cognitive Factors

CFA of the WMS-IV scores in our sample produced a 3-factor structure. Previous factor analyses of the Weschler Memory Scales have produced inconsistent factors due, in part, to the inclusion or exclusion of the immediate and delayed recall measures present in each test (see Bouman *et al.*, 2015). The present results are most consistent with the WMS-IV factor analysis performed by Hoezle and colleagues (Hoelzle *et al.*, 2011). This CFA was conducted on immediate and delayed recall subtests, excluding only the recognition subscores which were included in our study. Their findings supported a three-factor structure with a logical memory component, a verbal-paired associates component, and a visual attention component loaded highly by DE but also by SA and SSP scores. Meanwhile VR tests had similar moderate loadings in 2 of the 3 dimensions. While they acknowledge the issues with including both immediate and delayed subtests, their decision to do so was in effort to increase the number of marker variables for the CFA, noting that analyzing

only immediate or delayed subtests would likely not result in multivariate solutions due to a restricted number of variables. Indeed, a EFA on our own data set showed that only 1 component is extracted when only delayed scores are analyzed (not presented). Our CFA also included SA, SSP, and DE tests into a single factor. These tests share the similarity of incorporating grid and/or complex symbol memorization, with the DE test incorporating elements of the SA and SSP tests in their use of grids and abstract figures, respectively. Hoelzle *et al.* speculate that the inability to produce distinct visual memory and visual working memory factors as in the original WMS-IV CFA (Wechsler, 2009) was due to the small number of visual working memory variables (SA, SSP), as the ideal number to define a dimension are three (Hair Jr *et al.*, 2017). Our inclusion of a third variable in the recognition subscores did not significantly impact the factor structure compared to CFA of delayed and immediate subscores only, as evidenced by the relatively low loadings in recognition tests across all factors.

CFA of select tests from the D-KEFS battery, which measures EFs, returned a 4-factor structure. While the fit of this factor structure may be considered subpar from the perspective of certain fit index thresholds (Hu & Bentler, 1999), this likely is due to 2 factors containing only 2 indicators, which adds constraint to a model where three indicators per factor are considered ideal, as mentioned previously. Although EFs can be broken apart into distinct domains, factors are strongly intercorrelated, showing diversity but unity (Miyake & Friedman, 2012; Friedman & Miyake, 2017). A 3-factor structure of EFs was among the first extracted (Miyake *et al.*, 2000) and various studies have corroborated this 3-factor model in different age groups, while others have observed 2 factor structures, or a 1 factor structure describing a single common factor of executive function (for review see Karr *et al.*, 2019). Latzman *et al.* performed a CFA on the original D-KEFS standardization sample (Latzman & Markon, 2010). The authors found that a three-factor model provided optimal fit across all age groups with moderate correlations among the factors; these factors greatly resembled those produced in our CFA. Two of our factors, Conceptual Flexibility and Inhibition, are indicated by the same subtests. The primary difference in our factors is the splitting of the VF test into separate fluency and switching factors. The authors note that VF-LF and VF-CF loadings were relatively low in Monitoring, lending to the possibility that they are partially distinct from VF-CS and VF-CC, it is also likely that the inclusion of additional scores into the CFA had a profound impact on the factors extracted. The standardization sample also encompassed a broader age range (8-89) than our participants. Since increasing age weakens the

associations between the switch and fluency components of the VF tests, our older sample may extract fluency as a distinct EF influenced by the greater vocabulary of older adults (Unsworth *et al.*, 2011). Separation of verbal fluency into separate production and switching components has been reported before (Nutter-Upham *et al.*, 2008) with the authors believing that switching tasks may be distinct due to providing the participant additional lexical search cues. In general, the D-KEFS factors we obtained are mostly consistent with previous literature further validating their use as an indicator of cognitive performance.

In addition to cognitive measures, a CFA was performed on FA values of all prefrontal tracts to extract their common variance and reduce it into a single latent measure. These results suggest that these tracts, likely due to their proximity and anatomical similarities, could not be separated into further unique factors, indicating a high degree of inseparable common variance among these tracts. Since many prefrontal functions are considered to be spread diffusely across the PFC without strong evidence of subregion specificity (Stuss & Alexander, 2000; Fuster, 2001), examining broad prefrontal FA as a mediator was viewed as a good step prior to tract specific analyses. While the reduction of DTI measures from multiple tracts into a single factor is common (Penke *et al.*, 2010; Gazes *et al.*, 2016; de Mooij *et al.*, 2018; Chamberland *et al.*, 2019), this is the first study that did so on the WM of prefrontal subregions. The fit indices for the FA CFA were considerably poorer compared to those found in the cognitive task CFAs, although it still achieved adequate fit comparable to other studies that reduced tract FA (Cox *et al.*, 2016). In order to achieve fit, error terms of several tracts had to be covaried. The decision to covary certain tract error variances was based on model modification indices and theoretical considerations (Hermida, 2015). In our CFA, all medial tract error terms were covaried with one another (Figure 17). Due to tract proximity these medial tracts may have a sufficient degree of correlated error variance that needs to be accounted for. Error variances of tract DTI parameters have been correlated in the past even when the tracts were not within the same lobe or hemisphere. In a study by Lovden *et al.* numerous projection and association fibers required error terms to be covaried for the CFA of a single FA variable to achieve fit, as alternative models presuming error term independence failed to achieve fit (Lovden *et al.*, 2013).

4.09. Contributions of Age, Sex, and ICV on Cognitive Performance

Structural equation models were used to measure the effects of age, sex, and ICV on the general PFC FA factor as well as the direct effects these variables have on cognitive metrics. Just as HO modelling showed certain tracts were affected by ICV in addition to age, SEM analysis found that both age and ICV were associated with PFC FA, with older age and lower ICV predicting lower FA values.

SEM found direct effects of age in most cognitive scores. All relationships were measured using a linear model, with age predicting lower scores on D-KEFS and WMS-IV factors, and higher SRT and CRT, indicative of worse performance. A decline in cognitive performance with age across various domains, such as executive functions, memory, attention, and processing speed is well reported (Salthouse, 2010; Harada *et al.*, 2013). Large scale studies investigating age-related cognitive decline often include additional neuropsychological tests and generate latent cognitive factors different than those in our study, complicating the direct comparison of effects on cognitive performance across studies. However, comparisons with previous studies can still be made at the individual subtest level.

Using SEM, negative associations were observed between age and all WMS-IV factor scores, with particularly strong effects in visuospatial memory and verbal memory. Age-related declines in WMS-IV scores have been found both when organized into factors (Salthouse, 2009; Pauls *et al.*, 2013) as well as in individual subtests (Munro Cullum *et al.*, 1990; Uttl *et al.*, 2002; Haaland *et al.*, 2003). In addition to effects of age, visuospatial memory and logical memory was also associated with sex and ICV. In support of well documented sex differences in memory (Herlitz *et al.*, 1997; Lewin *et al.*, 2001; de Frias *et al.*, 2006; Bloise & Johnson, 2007), men performed better on visuospatial memory tests while women achieved higher scores in logical memory. Greater ICV predicted higher scores in both cases, while the exact mechanism behind this relationship is unclear, it may be due to oft reported correlations between larger head size and higher general intelligence (Gignac *et al.*, 2003; McDaniel, 2005; Rushton & Ankney, 2009; Pietschnig *et al.*, 2015).

In executive functions, SEM confirmed the negative association between age and Conceptual Flexibility scores, in agreement with previous studies which found age-related declines in performance on the D-KEFS sorting test (Mattioli *et al.*, 2014; Ishigami *et al.*, 2016), California Card Sorting Test (Beatty *et al.*, 1993; Saltzman *et al.*, 2000), and the Wisconsin Card Sorting Test (Rhodes, 2004; Miranda *et al.*, 2020). A strong negative association was found between age and the Inhibition factor, confirming known age-related slowing of trail making (Ashendorf *et al.*, 2008; Perry *et al.*, 2009) and color-word interference test (Davidson *et al.*, 2003; Van der Elst *et al.*, 2006; Rivera *et al.*, 2017) completion times. A significant, but weak, age-related decline was found in Verbal Fluency scores, supporting previous findings of declines in both letter (Tomer & Levin, 1993; Dursun *et al.*, 2002; Brickman *et al.*, 2005) and category fluency (Crossley *et al.*, 1997; Stolwyk *et al.*, 2015; Taler *et al.*, 2020).

After SEM, Verbal Switch was no longer associated with age but retained a sex difference with better performance in women. While several studies have found better performance in verbal fluency tasks in women compared to men (Bolla *et al.*, 1990; Acevedo *et al.*, 2000; Weiss *et al.*, 2003), these studies did not investigate the switching component of the test. One study that examined the switching component found similar results as in our study, with no age effects on verbal switching but a significant sex difference (Stolwyk *et al.*, 2015). The authors suggest that by receiving two search cues the task may decrease demands on working memory thus making the test easier for older adults. Older participants may also draw upon greater verbal intelligence and word knowledge.

As reported in previous studies (Dixon *et al.*, 2007; Dykiert *et al.*, 2012; Woods *et al.*, 2015) we confirmed the presence of an age effect on simple and choice reaction times. Mean SRT and CRT increased with age, indicative of increased response latency. The effects of age were also greater for the CRT than the SRT, which involves additional processing.

No differences due to age were found in RMET scores, with similar scores in young and old participants. While in agreement with previous studies finding no age effects (Castelli *et al.*, 2010; Cabinio *et al.*, 2015), recent large sample studies (Kynast *et al.*, 2020; Lee *et al.*, 2021) have found a decline in RMET scores with age. RMET scores were marked by significant sex differences, with women performing better than men. Sex differences in RMET scores have been noted since

the test's conception (Baron-Cohen *et al.*, 2001), and most studies investigating RMET performance find higher scores in women (Kirkland *et al.*, 2013; Vellante *et al.*, 2013).

After accounting for covariance between predictors, SEM found no effects of age, sex, or ICV on PASAT scores which were previously associated with these variables after simple correlational analysis. Most studies report PASAT scores decline with age and have no significant sex differences, although several studies have found no effects of age or higher scores with age (for review see Tombaugh, 2006); a few recent studies have also found sex differences with men outperforming women (Vanotti *et al.*, 2016; Sousa *et al.*, 2018). The majority of these studies did not perform multivariate analysis accounting for covariance between variables. A recent study found that demographic variables predict little variance in PASAT, with insignificant age and sex variables, and that the test is largely confounded by other factors such as participant anxiety and mathematical ability (Berard & Walker, 2021). Considering our sample is comprised mostly of educated adults this may account for the preservation of PASAT performance with age.

4.10. Contributions of Prefrontal FA on Cognitive Performance

The general PFC FA variable was not found to produce significant direct effects on any cognitive test studied. Consequently, no indirect effects between age or ICV to cognitive performance, with PFC FA acting as a mediator, were produced. To our knowledge no previous study has examined whether white matter integrity within prefrontal subregions has a mediating effect on age-related cognitive decline. Numerous studies that performed mediation analysis, or controlled for effects of age, have found WM integrity within the genu (Kievit *et al.*, 2014; Kuznetsova *et al.*, 2016; Fan *et al.*, 2018), anterior thalamic radiations (Kievit *et al.*, 2014; Cremers *et al.*, 2016), superior longitudinal fasciculus (Bendlin *et al.*, 2010; Gold *et al.*, 2010; Jacobs *et al.*, 2013), inferior longitudinal fasciculus (Cremers *et al.*, 2016), uncincate fasciculus (Salami *et al.*, 2012), and fronto-occipital fasciculus (Perry *et al.*, 2009; Salami *et al.*, 2012) to be associated with performance on various cognitive tasks, including those tested in this study. Less tract-specific analyses have also found whole-brain FA and frontal FA to mediate the effects of age on performance on a variety of tasks (Brickman *et al.*, 2006; Kennedy & Raz, 2009; Borghesani *et al.*, 2013; Haasz *et al.*, 2013). However, full mediation of WM integrity was not found, and

although significant associations between WM integrity and cognitive ability persisted after controlling for age, the effect sizes were greatly attenuated (Madden *et al.*, 2009), signifying that a large portion of the variance explained in performance by MW integrity is covaried with age.

Our results are in agreement with previous studies investigating frontal WM that found no direct effect of FA values on performance. Using SEM, Burgmans *et al.* found no direct effect of frontal FA on executive functions or processing speed; age remained as an independent predictor of cognitive performance with no significant indirect effect running though FA (Burgmans *et al.*, 2011). An aging study by Schulze *et al.* found that after controlling for age FA values within the DLPFC no longer correlated with working memory performance; however, frontal FA continued to correlate with functional MRI (fMRI) activation associated with working memory (Schulze *et al.*, 2011). Although prefrontal WM may not be directly associated with cognitive performance, age-related changes in WM may nonetheless contribute to GM changes that result in reduced performance with age. At least one study (Head *et al.*, 2008) found that although both prefrontal grey and white matter volumes decline with age, only GM volumes mediated the age-related decline in episodic memory while WM volumes did not. Additional studies investigating the interplay between prefrontal WM and GM, and their mediating effects of age-related cognitive decline, are required to properly discern these effects.

4.11. Mediation via Tract-Specific FA

Following testing of mediation for the general PFC FA, the mediative effects of individual tract FA values on age-related cognitive decline were examined. Although the general PFC FA had no significant effects, the FA values of certain orbitofrontal tracts did produce significant indirect effects of age or ICV on select cognitive scores.

A significant indirect effect of age was found on RMET performance. After accounting for the effects of age, FA values in the MOFCc were positively associated with RMET scores. Although age itself was not directly associated with RMET, age induced decline in MOFCc FA values contribute to reduced RMET scores. The RMET assesses theory of mind, the ability to infer the mental states of oneself and others (Stone *et al.*, 1998); the importance of the OFC to theory of mind has been well reported, lesion studies of the OFC have found impaired social judgement,

increased indifference, and reduced ability to recognize emotion (Stuss *et al.*, 2001; Beer *et al.*, 2003; Hornak *et al.*, 2003; Beer *et al.*, 2006). Functional neuroimaging studies have identified the OFC, especially the medial portions, as the most consistently activated region during theory of mind tasks (for review see Carrington & Bailey, 2009), in agreement with studies finding OFC GM volumes to be associated with theory of mind (Powell *et al.*, 2010). Neuroimaging with DTI has linked RMET performance with WM integrity (Charlton *et al.*, 2009; Cabinio *et al.*, 2015). Cabinio *et al.* found higher FA values in bilateral frontal areas, including inferior callosal fibers, to be associated with improved RMET performance. The significant mediative effect of the MOFCc on RMET is consistent with previous literature, reduced integrity of the WM in this region may impair normal functioning of the OFC, thus resulting in poorer RMET scores.

In addition to RMET, FA in the MOFCc also produced an indirect effect of age on CRT scores. Since age retains a positive direct effect on CRT this indicates that the effects of age on CRT are partially mediated by MOFCc FA, increased age leads to lower FA, leading to higher CRT. While reaction time is generally considered to be a non-specific measure, various lesion studies (Drewe, 1975; Leimkuhler & Mesulam, 1985; Stuss *et al.*, 2002; Alexander *et al.*, 2005) have consistently found patients with medial frontal lesions as performing worse on RT tasks. As choice reaction tasks involve additional processing to suppress attention or action, they introduce an element of inhibition to the task, further suggesting a frontal specificity. The SRT of patients with orbitofrontal lesions were especially slower when forced to simultaneously suppress distracting information (Whyte *et al.*, 1998); in another lesion study, in addition to right frontal lesions, those with lesions to the MOFC showed slower reaction times (Stuss *et al.*, 2005). The importance of the MOFCc to CRT has also been demonstrated with past DTI studies (Grieve *et al.*, 2007; Bucur *et al.*, 2008; Madden *et al.*, 2012) found higher FA values in the pericallosal white matter and CC genu to be associated with faster reaction times. Given the role the MOFCc plays in facilitating interhemispheric transfer of information in the PFC, the association of MOFCc FA with CRT performance appears reasonable. The function of the CC in transfering both motor commands and visual information from contralateral visual fields to both hemispheres has long been implicated as important for coordinating rapid reactions and attention (Posner & Petersen, 1990; Reuter-Lorenz & Stanczak, 2000).

Alongside the MOFCc, FA values in both the right and left LOFC also had significant direct effects with certain cognitive scores. FA values in the right LOFC produced a direct effect on visuospatial memory with higher FA values associated with higher visuospatial memory scores, this generated a significant indirect effect of age on visuospatial memory with right LOFC FA acting as the mediator. This mediative effect also extends to ICV; although ICV was not associated with visuospatial memory, greater ICV is associated with higher FA in the right LOFC, thus producing an indirect effect of ICV on visuospatial memory via FA.

Whereas visuospatial memory and visual working memory have been mainly attributed to the DLPFC (Petrides, 1992; 1995; Deco *et al.*, 2004; Barbey *et al.*, 2013; Diamond & Levine, 2018), the LOFC functions primarily in emotional decision making and reward learning (Kringelbach & Rolls, 2004; Jonker *et al.*, 2015); therefore, its role in mediating visuospatial ability is unexpected. However, the LOFC receives input from both auditory and visual modalities, and is associated with medial temporal lobe structures, which suggests it may play a role in the encoding and retrieval of memories (Zald, 2003; Kringelbach & Rolls, 2004; Petrides, 2007). Lesion studies in primates have found LOFC lesions affect visual recognition and association memory tasks which require short-term holding of objects during a delay period (Bachevalier & Mishkin, 1986; Kowalska *et al.*, 1991; Meunier *et al.*, 1997), however these lesions were not solely specific to the LOFC. A study examining LOFC lesions in humans determined the LOFC may have a role in selecting stimuli based on a feeling of 'rightness' in a guessing task (Elliott *et al.*, 2000); due to the complexity of visuospatial tasks, reliance on guessing the most appropriate answer may be frequent. In support of finding the LOFC relevant to visuospatial tasks, human Positron Emission Tomography (PET) studies have shown increased activation of the right LOFC during encoding of abstract visual information to memory (Frey & Petrides, 2000; Petrides *et al.*, 2002) with little or no significant activation in the DLPFC. In addition, Zald *et al.* found that the LOFC coactivated alongside the DLPFC in many fMRI studies involving memory, semantic monitoring, and discrimination, which may reflect regulation or inhibitory control of memory processes by these regions and that processing zones may extend further ventrally than reported in most literature (Zald *et al.*, 2014).

Studies linking orbitofrontal WM to memory processes are limited, the majority of studies focus exclusively on working memory and use differing means of memory evaluation. While FA, and

volumes, of frontal WM has been associated with working memory (Salat *et al.*, 2002; Kennedy & Raz, 2009), integrities of long association tracts are more commonly measured and related to working memory performance (Charlton *et al.*, 2010; Walsh *et al.*, 2011; Krogsrud *et al.*, 2018). While not specific to the LOFC, several of the tracts evaluated, such as the uncinate fasciculus and occipitofrontal fasciculus, contain fibers that terminate in the LOFC.

Considering the conflicting evidence on importance of LOFC to visuospatial memory, it is important to note the visuospatial memory factor includes both working memory and episodic memory tests. Factor analysis was not able to separate working memory as an individual factor, which may be more linked with DLPFC. We were unable to find any studies investigating LOFC function and specifically relating it to symbol span, spatial addition, and design tests.

In addition, alongside issues concerning prefrontal subregion delineation, there is also variability regarding nomenclature. Many studies reporting negative findings in the OFC limit their analysis to the MOFC, with LOFC often labeled as the ventrolateral PFC which may include sections considered to be the DLPFC in our study. Several fMRI studies have found the ventrolateral PFC to be activated during visual working memory tasks using fMRI (D'Esposito *et al.*, 1999; Stern *et al.*, 2000; Fletcher & Henson, 2001), which further complicates extricating the functions of the DLPFC and LOFC from one another.

4.12. Suppression via Tract-Specific FA

The remaining indirect effects involved the left LOFC were all characterized by inconsistent mediation, also known as suppression. As in the right LOFC, significant indirect effects of age and ICV on visuospatial memory also occurred with left LOFC FA as the mediating variable. However, left LOFC FA had a negative relationship with visuospatial scores, with higher FA values predicting lower scores; consequently, the indirect effects ran in the opposite direction of age and ICV direct effects, indicating inconsistent mediation.

These patterns were replicated in SRT and Conceptual Flexibility; higher FA values in the left LOFC predicted slower SRT and lower Conceptual Flexibility scores, with age and ICV indirect effects running opposite of their direct effects for these cognitive metrics. Simple reaction time

tasks are simpler than choice reaction time tasks, and deficits in SRT are similarly anatomically non-specific. DTI studies show a wide range of tract FA values predict reaction times (Tuch *et al.*, 2005) and these relationships vary between negative or positive depending on the tract analyzed. As mentioned previously with CRT, the influence of the OFC to reaction time has been documented, but with a greater focus on the medial rather than lateral regions.

Conceptual Flexibility, which is indicated by card sorting test scores, is also understudied with respect to LOFC functioning. Animal lesion studies of imperfect card sorting test analogues have found OFC damage affects set shifting and inhibition of previously learnt rules (Dias *et al.*, 1996; Bissonette *et al.*, 2008). OFC lesions in humans have been found to impair object alternation tasks (Freedman *et al.*, 1998; Zald & Andreotti, 2010) and produce less total correct sorts on card sorting tests. Imaging studies have primarily focused on set shifting and the DLPFC; however, a PET study has found that aside from DLPFC activation, the left LOFC activated during a matching task where the participant is tasked with maintaining the same sorting category and inhibit other sorting rules (Nagahama *et al.*, 1996). In addition to the dearth of literature focusing on the LOFC, the majority of card sorting studies focus on the number of perseverative errors made instead of total sorts. Conceptual Flexibility is indicated by total sorts, sort description, and sort recognition scores which are evaluations missing from these studies that may require the LOFC.

4.13. Interpretation of Suppressive Effects

The primary interest in mediation analysis is the presence of the indirect effect, whether the relationships that age has with cognitive performance are partially driven by age effects on FA values (Cheung & Lau, 2008; Pearl, 2014). In standard, consistent, mediation, some portion of total cognitive ability variance explained by age is from its direct effect and some from its indirect effect, with both effects having the same sign. This occurred in the 4 indirect effects summarized previously, where higher tract FA values predicted better cognitive performance. For the remaining 6 indirect effects involving the left LOFC, the opposite phenomenon is occurring, known as suppression (Zhao *et al.*, 2010). After accounting for the effects of age, FA is negatively associated with cognitive performance, resulting in an indirect effect opposite to the direct effect of age. Since increased age causes decreases in FA and cognitive performance, but lower FA is

linked with increased cognitive performance, the indirect and direct effects counteract each other; as age increases, cognitive performance increases, because FA decreases. This effect was also found to occur in the second demographic variable considered, ICV. Since higher ICV values are linked with greater FA, and greater FA with worse cognitive performance, the indirect effect of ICV on cognitive performance is negative, where higher ICV is linked with worse scores. Although in Conceptual Flexibility and SRT there was no significant direct effect of ICV on these scores, there is a significant indirect effect, meaning that ICV influences these variables solely due to FA while age has effects both independent of, and resulting from, its relationship with FA. In these cases, mediation is not occurring. The relationship age has with cognitive performance does not have a portion that runs through FA. Tract-specific FA is instead acting as a suppressor, or enhancer, variable (Pandey & Elliott, 2010). These are variables which obscure the true effect of the independent variable on the dependent variable, or criterion, by reducing its effect size. By accounting for these variables through mediation analysis, the independent variable can be 'purified' of its criterion-irrelevant variance associated with the suppressor and strengthen the relationship it has with the dependent variable (Tzelgov & Henik, 1991; Maassen & Bakker, 2001), increasing the model R^2.

While suppression is occasionally observed in psychological research, investigations into potential suppressive effects of neuroanatomical variables are seldom seen, and such effects may be intentionally unreported. However, negative effects involving WM integrity, in which higher FA is associated with worse cognitive performance, have been observed before. A longitudinal study by Bender *et al.* found that although higher baseline FA predicts improved associative memory, FA declines and RD increases over a 2-year period were associated with improved memory at a follow-up examination (Bender *et al.*, 2016). The authors suggest that decreases in FA may reflect development of crossing fibers and fiber reorganization in healthy WM and not be indicative of pathology. While FA is believed to reflect axonal directionality, orderly fiber arrangement is not common to cerebral white matter; therefore, interpreting these changes in FA as loss of integrity may be misleading. SWM, which is poorly myelinated and has complex fiber architecture, may be further vulnerable to these effects (De Santis *et al.*, 2014). The FA measures in prefrontal voxels may be less indicative of myelination and single fiber integrity and instead measure water diffusion in the presence of highly heterogenous fiber orientations (Madler *et al.*, 2008; Jeurissen *et al.*, 2013; Billiet *et al.*, 2015). More recently, Webb and colleagues investigated the effects of age on

frontostriatal WM and executive functions in healthy adults across the lifespan. While age was associated with a linear decline in FA and EFs, multivariate modeling found a significant interaction term where higher tract FA was associated with poorer EF scores (Webb *et al.*, 2020). However, this effect was not found in the oldest participants. Webb *et al* reason that since lower FA is seen as beneficial during development, the younger adults may be in a protracted development stage that will produce peak FA values after 30 years of age, with higher EF scores associated with lower FA in the young.

While the above studies highlight cases where high FA predicted worse cognitive performance, they did not use pathway analysis to determine whether FA produced a significant suppressive indirect effect. Our study is the first to report the presence of such effects specific to WM within the left LOFC; however, why this specificity to the left LOFC occurs is unclear. The only tracts whose FA values generated significant indirect effects were those in the OFC, these mediating tracts were also those least affected by age, while the superior tracts more affected by age did not produce any indirect effects. In addition, the differential effects of the left and right LOFC on visuospatial ability may reflect partial laterality of visuospatial ability to the right hemisphere (Corballis, 2003). The remaining variance in OFC FA unmodeled by age is associated with cognitive performance, which implies that these interindividual differences in FA that predict cognitive ability are unrelated to age and may be suggestive of age unrelated pathology or fiber reorganization. The latter is further supported by the significance of ICV indirect effects despite no significant direct effects existing between ICV and cognitive performance. FA values of the LOFC tracts are predicted by ICV, therefore macrostructural changes in organization may drive changes in cognitive performance.

Lastly, it is important to consider that when FA values of all tracts were reduced to a single latent variable no indirect effects occurred, the mediation effects of single tracts were drowned out by other tracts' lack of association with cognitive performance. While single tract analysis may provide us with more anatomical specificity, it is more vulnerable to measurement error associated with that tract, which may lead to modelling of noise and impact results.

4.14. Limitations and Future Directions

There are numerous limitations to consider in this study. Images were obtained on a 1.5T scanner with 30 diffusion directions while most modern research scanners operate at 3T and provide greater resolution and signal-to-noise ratio. As mentioned previously, this makes delineation of specific PFC gyri difficult and, consequently, our segmentation protocol did not use individual gyri as landmarks during ROI placement. Tractography involving a single diffusion tensor, as in this study, is also susceptible to partial volume and crossing fiber effects (Jeurissen *et al.*, 2013); resulting FA values may not be as informative about degree of myelination or axonal integrity (Jones *et al.*, 2013; De Santis *et al.*, 2014). It is therefore important not to attribute changes in microstructural parameters to actual histological changes in WM (Beaulieu, 2014). While the use of more advanced tractography protocols not reliant on a single diffusion tensor mitigate these issues (Jeurissen *et al.*, 2019), no method is perfect and free from crossing fiber effects (Schilling *et al.*, 2019).

Additionally, while all participants were healthy adults with no neurological contraindications, we did not control for all conditions that may contribute to WM damage. Potentially hypertensive participants were not excluded, and high blood pressure has been linked to brain atrophy and cognitive deficits (Raz *et al.*, 2007; Filley & Fields, 2016). Cardiovascular problems are also associated with increased white matter hyperintensities (WMH) which were not controlled for in this study (Wardlaw *et al.*, 2015). WMH increase with age, are prominent in the frontal lobe (Tullberg *et al.*, 2004; Fazekas *et al.*, 2005; Yoshita *et al.*, 2006) and have been linked to reduced cognitive performance (Bennett & Madden, 2014; Boutzoukas *et al.*, 2021). Taking participant WMH load into consideration as an additional predictor of cognitive performance may have affected our results. However, a general limitation of healthy aging studies is that the sample of older adults who meet exclusion criteria may fail to capture the vast variability in the aging process and not be representative of the actual elderly population. Since WMH are found in healthy adults, including the non-elderly, it remains unclear how WMH should be unbiasedly considered or controlled for in aging studies.

The study did not perform post-hoc tests for DTI parameter regression models adjusting for multiple comparisons. However, our previous study (Malykhin *et al.,* 2011) already determined that PFC WM, as measured by FA, MD, AD, RD, and volume, is affected by age. The investigation

of the less often cited measures is exploratory in nature, but nearly 80% of models in the additional parameters of fiber count, fiber length, and fibers per voxel survive Holm-Bonferroni correction and do not drastically alter the takeaways of this study, as the presence of weak or near-insignificant effects was mentioned and all microstructural models remain significant.

A limitation of covariance-based SEM used in this study is that it assumes linear relationships between variables and works best when variables follow a normal distribution (Hair Jr *et al.*, 2017). Future studies could use more sophisticated or alternate techniques such as partial least squares SEM (Lowry & Gaskin, 2014) which does not require data to conform to particular distributions and is more robust to violations.

To maximize power, all participants that completed individual cognitive tests were included in analysis; however, not all participants completed D-KEFS or WMS-IV testing, making direct comparison between cognitive domains challenging due to different sample sizes. Cognitive domains in memory and executive functions may also be sensitive to aging, with older subjects having higher or lower loadings to factors, or different factors altogether, compared to young subjects. However, in order to perform analysis of effects across the lifespan, cognitive factors must be calculated identically for all participants. Furthermore, D-KEFS and WMS-IV tests had additional assessments omitted in this study, such as counting errors made in the sorting and color-word interference tests.

Finally, the study is cross-sectional and cannot account for intraindividual variations in WM integrity. Although we tested for mediation using SEM, the cross-sectional design still precludes observation of causality. A longitudinal study would be required to determine whether individual changes in DTI metrics over several years predict age-related cognitive decline.

In addition to incorporating longitudinal designs with more advanced tractography and statistical analysis, future studies should aim to produce a more comprehensive assessment of cognitive functioning using more neuroimaging variables. The inclusion of parameters such as cortical thickness, GM volumes, WMH, and fMRI data into SEM would allow for the investigation of more complex interdependent relationships and their effects on cognitive performance. Given our findings, WM within the PFC should be studied in more detail; instead of focusing on large WM

tracts or the DLPFC, the role of the OFC on cognitive performance should be investigated further and extended to traditional OFC tests such as theory of mind and reward processing tasks.

4.15. Conclusion

DTI-tractography was used to study the effects of aging on prefrontal WM integrity. Higher order polynomial regression modelling found that all prefrontal subregions are affected by age, with decreases in FA, fiber count, and tract volume, and increases in MD, AD, and RD with advanced age. Relationships with age are predominantly non-linear but not uniform across subregions, with the MPFC more affected by age and the LOFC least affected.

The role prefrontal WM integrity has on mediating age-related cognitive decline was also investigated using SEM. Although increased age was associated with worse cognitive performance, FA values in prefrontal subregions were mostly unrelated to cognitive ability, and a latent factor of all subregions produced no significant direct or indirect effects. Although a general PFC FA variable was insignificant, FA values of OFC tracts did produce indirect age effects on RMET, SRT, CRT, visuospatial memory, and Conceptual Flexibility scores. While these effects were consistent in the MOFCc and right LOFC tracts, with FA values partially mediating age-related cognitive decline, the indirect effects were inconsistent in the left LOFC indicating a suppression effect.

The study highlights the differences due to age in prefrontal WM anatomy and the effects these differences have on cognitive functioning, underscoring the important of using higher order modeling and SEM in estimating the interactions between age, cognitive performance, and measures of WM integrity.

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