From the Institute of Anatomy I
at Heinrich Heine University Düsseldorf

White matter changes and executive functions in ageing

Dissertation

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submitted by
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For Kevin

You can't help getting older, but you don't have to get old.

George Burns

Zusammenfassung

Wie in der Literatur umfassend beschrieben, sind Alterungsprozesse mit Veränderungen der weißen Substanz assoziiert. Die meisten Studien dazu basieren jedoch auf kleinen Stichproben oder Querschnittsuntersuchungen. Aufgrund individueller Unterschiede ist es wichtig, diese Veränderungen bei einzelnen Personen zu untersuchen, anstatt sie über verschiedene Personen hinweg abzuleiten. Daher wurden sowohl Querschnitts- als auch longitudinale Veränderungen der weißen Substanz bei denselben Individuen im Alter von 18 bis 84 Jahren (N = 399) analysiert. Zur Messung altersbedingter Veränderungen in den Nervenbahnen wurden sowohl Diffusions-Tensor-Bildgebung (DTI) als auch Neurite Orientation Dispersion and Density Imaging (NODDI) verwendet. Die Ergebnisse zeigen erstens, dass Alterungseffekte, gemessen durch fractional anisotropy (FA), mean diffusivity (MD) und intra-cellular volume fraction (ICVF), in der weißen Substanz sichtbar sind, wenn man junge und ältere Erwachsene im Querschnitt vergleicht. Zweitens zeigen sich diese Effekte auch longitudinal, jedoch nur in Form von Veränderungen der Axone und Dendriten, gemessen durch ICVF. Drittens treten diese Effekte bei Personen ab 55 Jahren weder im Querschnitt noch longitudinal auf, was darauf hindeutet, dass das Alter allein keinen wesentlichen Einfluss auf den mikrostrukturellen Abbau im höheren Alter hat. Zusätzlich wurden Zusammenhänge zwischen Veränderungen der weißen Substanz und exekutiven Funktionen untersucht. Signifikante Korrelationen fanden sich bei longitudinalen Veränderungen in der linken *Capsula interna*, was deren anatomische Bedeutung für exekutive Funktionen unterstreicht. Zudem zeigten sich Zusammenhänge zwischen dem Zustand der weißen Substanz und Veränderungen der exekutiven Funktionen, insbesondere bei Assoziations-, Projektions- und *Corpus Callosum*-Fasern, gemessen durch den DTI-Parameter MD. Diese Veränderungen sind vermutlich auf ein Zusammenspiel von Risikofaktoren und Schutzmechanismen, wie Lebensstil und physiologische Einflüsse, zurückzuführen. Die Heterogenität der mikrostrukturellen Veränderungen der weißen Substanz spielt dabei eine Rolle für kognitive Veränderungen im Alterungsprozess.

Summary

It is extensively reported in literature that age is associated with white matter changes. However, these are mainly from studies with small sample sizes or studies that are cross-sectionally designed. Given inter-individual variability, it is important to study these changes within individuals rather than infer the trajectory of these changes across individuals. Thus, cross-sectional and longitudinal white matter changes were analysed on the same individuals aged 18 to 84 years ($N = 399$). To measure ageing effects on white matter tracts, both diffusion tensor imaging (DTI) and Neurite Orientation Dispersion and Density Imaging (NODDI) models were utilised. The findings indicate that first, ageing effects measured by fractional anisotropy (FA), mean diffusivity (MD), and intra-cellular volume fraction (ICVF) are evident in the brain's white matter tracts if inferred cross-sectionally in young to older adults. Secondly, these ageing effects are evident longitudinally but only in neurite density changes measured by ICVF. Thirdly, these effects are not evident among adults who are 55 years old and above neither cross-sectionally nor longitudinally, indicating that age in itself does not have a major impact on brain microstructural decline in older age. White matter changes were also explored in relation to changes in executive functions among older adults. Significant changes between executive functions were associated with longitudinal changes in the left internal capsule, reflecting the anatomical relevance of the internal capsule in the performance of executive functions. Brain state and changes in executive functions were also explored and the integrity of the association, projection, and callosal fibres were associated with greater changes in executive functions over time as shown by the DTI parameter MD. Potentially driven by various risks and protective factors such as lifestyle and physiological factors, heterogeneity of white matter microstructural changes likely play a role in changes in executive functions in ageing.

List of Abbreviations

ACR	anterior corona radiata
AIC	anterior limb of the internal capsule
CCG	cingulum at the cingulate gyrus area
CH	cingulum at the hippocampus area
CNR	contrast-to-noise ratio
CSF	cerebrospinal fluid
DTI	Diffusion Tensor Imaging
DTI-TK	Diffusion Tensor Imaging ToolKit
FA	fractional anisotropy
FSL	FMRIB Software Library
ICVF	intra-cellular volume fraction
KMO	Kaiser-Meyer-Olkin Measure of Sampling Adequacy
MD	mean diffusivity
NODDI	Neurite Orientation Dispersion and Density Imaging
ODI	orientation dispersion index
PCA	principal component analysis
PCR	posterior corona radiata
PIC	posterior limb of the internal capsule
PTR	posterior thalamic radiation
QUAD	QUality Assessment for DMRI
SQUAD	Study-wise QUality Assessment for DMRI
SCR	superior corona radiata
SD	standard deviation
SLF	superior longitudinal fasciculus
SNR	signal-to-noise ratio
SS	sagittal stratum
TBSS	Tract-based Spatial Statistics
TFCE	Threshold-Free Cluster Enhancement
UNC	uncinate fasciculus

Table of contents

1 Introduction

Increasing age leads to changes in brain structure and cognition. Structurally, there is a decrease in regional- and whole-brain volume, brain weight, cortical thickness, as well as ventricular expansion in older age (Anderton, 2002; Esiri, 2007; Salat et al., 2004; Scahill et al., 2003). While brain atrophy is reportedly due to a decrease in both grey and white matter volume, it has been suggested that white matter changes, in particular, signal the beginning of the normal ageing process (Ge et al., 2002). White matter volume decreases significantly in older adults (Farokhian et al., 2017; Ge et al., 2002; Guttmann et al., 1998) and this is likely due to morphological changes in axons and dendrites, collectively known as neurites. In particular, neurites undergo a reduction in length and number, demyelination, and decreasing length of myelinated fibres (Dickstein et al., 2013; Fjell and Walhovd, 2010; Marner et al., 2003; Pannese, 2011; Xie et al., 2016).

Brain structural decline may be accompanied by reduced performance in certain aspects of cognition. It is argued that structural decline of white matter pathways is partly responsible for this later-life cognitive decline because it leads to disconnection between neurons and therefore information transfer efficiency is reduced (O'Sullivan et al., 2001). Furthermore, there is evidence to support that white matter integrity mediates the association between age and cognitive performance, particularly higher order abilities and processing speed (e.g., Borghesani et al., 2013). On the other hand, a review by Bennett and Madden (2014) concluded that brain-behaviour relationship is weaker when age is controlled for and therefore age mediates the effect of white matter integrity on cognitive performance. Given conflicting evidence, it is still unclear whether white matter integrity mediates the relationship between cognitive performance and age or age mediates the relationship between white matter integrity and cognitive performance.

Cognitive decline in older age is particularly evident in terms of executive functions which comprise several aspects of cognition such as reasoning, strategic encoding, information retrieval, learning or responding to novel information, inhibition, and task-switching (Park et al., 2001). These also support other tasks such as language processing and language production (Higby et al., 2019). In older age, executive functions are associated with the ability to independently engage in activities of daily living (Cahn-Weiner et al., 2002). Decline in executive functions are considered a key feature or hallmark of cognitive ageing. During the second decade of life, executive functions start to decline but its cumulative effect gains prominence only in late adulthood (Park et al., 2001).

Given the prominent role of executive functions in ageing, it is important to study the relationships between age, executive functions, and white matter changes. While it is widely

reported that white matter changes occur in ageing, there is a range of variability as well as mixed evidence on the nature of these changes based on cross-sectional and longitudinal observations. Given an increasingly ageing population (United Nations, 2017), further clarification and understanding of these changes are needed. It is therefore important to examine these changes and differences and compare these cross-sectionally and longitudinally.

The following sections will outline how white matter changes or differences are measured *in vivo*, important cross-sectional observations on white matter differences and longitudinal observations on white matter changes in ageing, and the relationship between these white matter changes and executive functions in older adults.

1.1 Measuring white matter in vivo

Diffusion tensor imaging (DTI; Basser and Pierpaoli, 1996) is typically used to characterise white matter changes or differences *in vivo*. From the DTI model, the movement of water molecules in the brain are used to infer the underlying white matter architecture (Jones, 2008). In brain tissue, water molecules diffuse faster along the length of the axons compared to diffusion perpendicular to it. When molecules move randomly in any direction, diffusion is described as isotropic whereas when molecules move preferentially in a certain direction, diffusion is described as anisotropic. The degree of anisotropy is measured by the DTI parameter fractional anisotropy (FA; Pierpaoli and Basser, 1996) whose values range from 1 (i.e., diffusion is highly anisotropic) to 0 (i.e., diffusion is highly isotropic). High FA values are typically observed in fibre bundles with a common orientation such as the corpus callosum. This is illustrated in Fig. 1 below. High FA values may indicate that the white matter tracts are highly aligned, that there is potentially a high degree of myelination or that there is dense axonal packing (Beaulieu, 2002). In the developing brain, high FA values may indicate white matter maturation (Lebel and Beaulieu, 2011). Low FA values could indicate axonal degeneration or demyelination due to normal ageing or due to the presence of neuropathology such as multiple sclerosis (Alexander et al., 2007). However, it is important to note that although FA is sensitive to microstructural changes, it is a non-specific summary measure of microstructural integrity (Alexander et al., 2011). It is therefore unable to distinguish which specific biological change contributes to a change in FA values. Low FA can also come from non-biological factors such as low signal-to-noise ratio (SNR), artefacts (e.g., misregistration of diffusion-weighted images from eddy currents or head motion), partial volume effect where the average FA in a voxel consists of signals from, for example, grey matter, white matter, and cerebrospinal fluid (CSF), and regions of crossing white matter tracts (Alexander et al., 2007; Alexander et al., 2011).

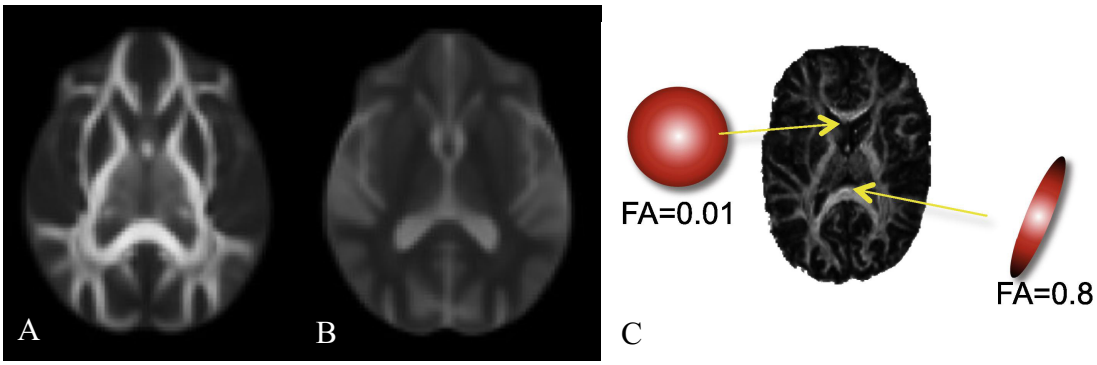

Fig. 1: (**A**) Example of FA diffusion map. (**B**) Example of MD diffusion map. Images A and B are taken from Motovylyak et al. (2022). (**C**) Higher FA values are found in white matter bundles that are highly aligned such as the corpus callosum, where diffusion is described as anisotropic. Lower FA values are found in areas such as the ventricles, where diffusion is described as isotropic. Isotropic diffusion is typically represented by a sphere whereas anisotropic diffusion is typically represented by an ellipsoid. Image C is taken from Walhovd et al. (2014).

Another DTI parameter is the mean diffusivity (MD) which refers to the overall, average diffusion regardless of direction (Heiervang et al., 2006). Biologically, it is an inverse measure of membrane density and fluid viscosity (i.e., the lower the membrane density and fluid viscosity, the higher the MD) and it is sensitive to the number of cells in the tissue (cellularity), the presence of edema, and necrosis (Alexander et al., 2011). For example, cytotoxic edema may lead to a decrease in MD (Lin et al., 2016; Ogawa et al, 2018; Rai et al., 2008) while vasogenic edema may lead to an increase in MD (Lin et al., 2016; Nuninga et al., 2020).

While there are other DTI parameters such as axial and radial diffusivity, FA and MD are most commonly used in studies and therefore the focus here is on these two parameters. In older adults, increasing age is associated with decreasing FA and increasing MD which putatively reflect white matter structural decline (Bennett et al., 2010; Borghesani et al., 2013; Cox et al., 2016; Raghavan et al., 2021; Sullivan and Pfefferbaum, 2006).

Although FA and MD have been shown to be sensitive to age effects on underlying white matter microstructures (Lawrence et al., 2021), these measures are non-specific and do not distinguish the different contributors of the diffusion signal such as axon diameter, axon density, axon orientation dispersion, and degree of myelination (Alexander et al., 2007; Pierpaoli et al., 1996). To disentangle the different sources of the diffusion signal, advanced biophysical models have been developed. One of these models is the Neurite Orientation Dispersion and Density Imaging (NODDI; Zhang et al., 2012) which was developed to provide specific measures such as neurite density and orientation dispersion. In this model, the intra-cellular volume fraction (ICVF) and the orientation dispersion index (ODI) are the most

commonly used parameters to measure white matter changes. The parameter ICVF is used as an index of neurite density while ODI provides a measure of tract complexity or tract fanning. Examples of ICVF and ODI maps are shown in Fig. 2.

There is a lack of investigation on the biological and cognitive correlates of the NODDI parameters in healthy adults. These relationships are likely shown in pathology, of which several studies exist. For example, in Alzheimer's disease, ICVF is reduced in parieto-occipital white matter and this correlated with visuospatial and visuo-perceptual cognitive performance (Slattery et al., 2017). In Sickle cell anaemia, positive correlation was found between ICVF and speed of processing, particularly ICVF in widespread regions that extend throughout the corpus callosum, corona radiata, and superior and inferior longitudinal fasciculi (Stotesbury et al., 2018). On the other hand, lower ODI in white matter lesions is associated with cognitive impairment in multiple sclerosis, possibly due to loss of axons and other microstructures such as astrocytes, oligodendrocytes and microglia, therefore reducing the white matter structural complexity (Preziosa et al., 2023).

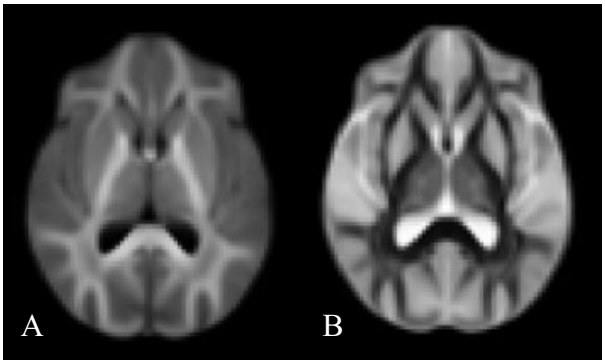

Fig. 2: (**A**) Example of ICVF diffusion map. (**B**) Example of ODI diffusion map. Image from Motovylyak et al., 2022.

It has been demonstrated that NODDI parameters can indeed provide more specific insights on biological processes in ageing compared to DTI parameters (Raghavan et al., 2021; Timmers et al., 2016). For example, evidence show that ICVF and ODI parameters do not have overlapping contribution to FA values but both independently overlap with FA, indicating separate contribution to FA values (Timmers et al., 2016). It provides evidence that FA values contain contributions from neurite density and the tract's orientation dispersion and that the NODDI model can disentangle these two contributors to FA. Furthermore, histological measures of tract orientation dispersion are more strongly correlated with ODI than with FA (Grussu et al., 2017; Schilling et al., 2018), indicating that the ODI parameter is a more specific

measure of tract orientation than FA. In addition to specificity, it has also been demonstrated that the NODDI model, like DTI, has sensitivity to age effects on white matter tracts particularly in older adults with higher risk of Alzheimer's Disease but nonetheless healthy (Motovylyak et al., 2022). The ODI parameter, in particular, was found to be most sensitive to age (Beck et al., 2021).

1.2 Cross-sectional white matter differences

Much of the knowledge about white matter changes in ageing comes from cross-sectional studies. The main findings from majority of these cross-sectional studies (e.g., Bendlin et al., 2010; Jernigan et al., 2001; Salat et al., 2005; Sullivan & Pfefferbaum, 2006) found that decrease in FA values are greater in the frontal lobe area, indicating an anterior to posterior age-related decline where anterior fibre tracts show more susceptibility to age-related degeneration in comparison to posterior tracts (Sullivan et al., 2010a). Furthermore, tracts that traverse the frontal and parietal cortices (e.g., the uncinate fasciculus and the cingulum bundle) showed greater decline in the anterior portion compared to the posterior portion (Davis et al., 2009). Age-related differences in FA were also found to occur first in the frontal area, particularly in the cingulum, as opposed to the posterior part of the brain (Yoon et al., 2008), which is also indicative of an anterior to posterior gradient of age-related changes in the brain. Evidence further suggests that throughout the brain, there is regional variation in age-related decline although the corpus callosum typically exhibits the anterior-posterior gradient (Sullivan et al., 2010b; Voineskos et al., 2012). Other patterns of age-related decline have also been described by Burzynska and colleagues (2010). These patterns include a decrease in FA accompanied by a decrease in MD which was observed in parts of the corticospinal tracts at the level of the posterior limb of the internal capsule as well as in the cerebral peduncles in the midbrain. This is possibly due to gliosis or early axonal injury. Another pattern of change observed in ageing is a decrease in FA without a significant difference in MD and this is considered to be due to axonal loss and increases in glial cells. Moreover, evidence suggests that MD is most sensitive to ageing (Raghavan et al., 2021; Slater et al., 2019) although this finding could potentially be driven by partial volume effects due to MD's susceptibility to CSF contamination (Cox et al., 2016). In a mixed cross-sectional and longitudinal study, FA was found to be the most sensitive to ageing among other conventional DTI metrics (Beck et al., 2021).

On the other hand, the NODDI model has gained popularity in investigating white matter changes in disease but there has been limited studies on white matter changes in the healthy ageing population. Among the few studies is a large cross-sectional study by Cox and

colleagues (2016) on healthy UK Biobank participants which used both NODDI and DTI to investigate the association between age and major white matter tracts. In this study of 3,513 elderly participants, older age was significantly associated with lower FA, higher MD, lower ICVF indicating lower neurite density, and lower ODI indicating less tract dispersion. These relationships between age and diffusion parameters were observed in the forceps minor, anterior, posterior, and superior thalamic radiations, and association fibres such as the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus. Similarly, Raghavan and colleagues (2021) found increasing age to be associated with decreased FA, increased MD, and lower neurite density. Furthermore, it was found that depending on tract tortuosity and the presence of crossing fibres, ODI either increased or decreased. In the corpus callosum, ODI decreased as age increased. This indicates reduced tract complexity, possibly due to loss of fibres. However, ODI increased in the fornix, cingulum, and parahippocampal cingulum, indicating greater tract complexity possibly due to greater loosening, fanning, or bending of the white matter fibre bundle in older age (Raghavan et al., 2021). In the corticospinal tract, there is evidence for decreasing ODI with increasing age in older adults (Gozdas et al., 2021) whereas increasing ODI with increasing age was observed among young to middle-aged adults (Kodiweera et al., 2016). There are also studies that report no significant ODI age effects (e.g., Merluzzi et al., 2016; Motovylyak et al., 2022).

The relationship between NODDI and DTI parameters in ageing have also been described cross-sectionally. It has been shown that an increase in neurite density in the first two decades of life could drive the increase in FA while the increase in ODI drive the decrease in FA in later decades of life (Chang et al., 2015). Cox and colleagues (2016) found that the decline in FA in older age is explained predominantly by the decline in ICVF rather than changes in ODI. This implies that changes in neurite density in ageing contributes more to changes in FA than changes in tract complexity, making it more sensitive to ageing. This is in contrast to another finding where ODI was found to be most sensitive to ageing (Kodiweera et al., 2016). These were, however, observed among young to middle-aged adults and may not be applicable to older adults. Notwithstanding, in ageing as well as in disease (see Kamiya and colleagues (2020) for review), it is possible to observe either an increase, decrease, or no change in ODI, depending on tract tortuosity and the presence of crossing fibres (Raghavan et al., 2021). In the study by Raghavan and colleagues (2021), MD and neurite density were found to be strongly associated across tracts, except in the fornix, possibly due to CSF partial-volume contamination. On the other hand, FA and ODI were strongly associated in the association tracts, anterior limb of the internal capsule, and inferior temporal white matter. This meant that as the neurite density decreased, MD increased and as the tract dispersion increased, FA decreased.

1.3 Longitudinal white matter changes

White matter changes can be detected by DTI over a relatively short period of time (Charlton et al., 2010). Over a period of two years, widespread longitudinal decrease in FA and increase in MD were found across the whole brain (e.g., Barrick et al., 2010; de Groot et al., 2016). These longitudinal changes were more pronounced among older adults than in younger adults (de Groot et al., 2016). Furthermore, Sexton and colleagues (2014) observed accelerated decline in FA and an increase in MD among older adults with a higher annual rate of change among those who were approximately on their fifth decade of life. These effects were evident in the frontal as well as parietal lobes. This is in contrast to previous findings by Barrick and colleagues (2010) who found no evidence of accelerated decline in the frontal lobe regions during a 2-year period. Although both studies have a similar methodological approach, the study by Barrick and colleagues (2010) had fewer and older participants (N = 84; mean age = 71 years) compared to the study by Sexton and colleagues (2014), which had 203 participants with a mean age of 53 years. These could potentially account for the contrasting results in the rate of decline. In another longitudinal study, a decrease in FA in ageing was found in the corpus callosum, the left anterior limb of the internal capsule, left external capsule, left and right corona radiata, and left superior longitudinal fasciculus (Coelho et al., 2021).

Although there is some cross-sectional evidence on the association between age and differences in neurite density and tract complexity in healthy individuals, as mentioned in the previous section, there is a dearth of evidence on how these change within the individual over time. Longitudinal studies using the NODDI model largely focus on pathology or acquired brain injury. Since individual trajectories were largely inferred from cross-sectional data, there is a need for an investigation of intra-individual changes in healthy ageing.

1.4 Relationship between white matter changes and executive functions in ageing

Changes in region-specific white matter microstructure have been linked to changes in executive functions. For example, it has been demonstrated in a study combining DTI and structural equation modelling that the integrity of the splenium of the corpus callosum predicted performance of executive functions (Voineskos et al., 2012). White matter changes may occur in conjunction with functional changes in the brain that are associated with the performance of executive functions (see Bennett and Madden, 2014 and Spreng et al., 2017 for reviews). Interestingly, it has also been shown that structural changes in white matter connectivity and not changes in functional connectivity account for age-related decline in executive functions (Fjell et al., 2017b).

Since white matter microstructural changes are typically investigated using the DTI model, the parameters FA and MD are commonly used to demonstrate the global effects of ageing on white matter and its relationship to executive function. Increasing MD and decreasing FA were shown to accompany a decline in executive functions (Charlton et al., 2006; Coelho et al., 2021) with age effects observed on the association between executive function and FA from the frontal and parietal white matter tracts to the thalamus (Grieve et al., 2007). In contrast, Charlton and colleagues (2010) found no significant change in executive function in a 2-year interval despite significant change in the DTI parameters. It was argued that either executive functions are stable during this 2-year period or that practice effects may have cancelled out the potential ageing effects. Controlling for age, performance of executive functions, measured in response times, correlated negatively with FA in the left superior longitudinal fasciculus and right uncinate fasciculus (Sasson et al., 2013). A shorter response time is related to higher FA which in turn indicates better white matter integrity. Poorer executive functions were also associated with lower FA in the anterior and posterior cingulum, as well as in the inferior longitudinal fasciculus (Kantarci et al., 2011).

Investigation of ageing effects and executive functions using the NODDI model is limited. A study by Merluzzi and colleagues (2016) found that reduced neurite density in the dorsomedial prefrontal cortex and the ventromedial prefrontal cortex predicted poorer executive function performance. In another study on late-middle-aged adults (mean age = 64 years), neurite density in the cingulum adjacent to the cingulate cortex predicted executive function performance (Motovylyak et al., 2022). Both studies are cross-sectional in nature and therefore unable to capture white matter changes over time. The relationship between these changes in NODDI parameters and in executive functions in older age remain to be investigated. Changes in white matter microstructure as well as changes in executive functions need to be observed longitudinally.

1.5 Aims and Hypotheses

In these data-driven studies, the first study aimed to examine and compare both longitudinal and cross-sectional white matter changes on major projection and association fibre tracts, specifically the superior corona radiata, anterior corona radiata, posterior corona radiata, anterior limb of the internal capsule, posterior limb of the internal capsule, superior longitudinal fasciculus, posterior thalamic radiation, sagittal stratum, uncinate fasciculus, cingulum at the cingulate gyrus area, and cingulum at the hippocampus area. To assess these changes, the DTI

parameters FA and MD were used as well as the NODDI parameters ICVF for neurite density and ODI for tract complexity.

While the studies did not aim to compare the DTI and NODDI approaches to white matter changes in ageing, the NODDI model was employed to go beyond general observations from the DTI model (i.e., to add more specific observations by measuring changes in neurite density and tract orientation dispersion). Furthermore, the studies focused on ageing and therefore, white matter changes among the older adult group were of particular interest. These changes were therefore examined among older adults aged 55 years onwards. To see how age effects are observed when younger adults are included in the group, these changes were also examined across adulthood (i.e., from young to older adults). It was hypothesized that age effects are significantly different between cross-sectional and longitudinal observations.

Given that the focus is on ageing and putative age-related brain structural decline occurs in older adults (Westlye et al., 2010), the second study examined the relationship between white matter changes and executive functions in older adults aged 55 years and above. As in the first study, these changes were examined on major projection and association fibre tracts, specifically the superior corona radiata, anterior corona radiata, posterior corona radiata, anterior limb of the internal capsule, posterior limb of the internal capsule, superior longitudinal fasciculus, posterior thalamic radiation, sagittal stratum, uncinate fasciculus, cingulum at the cingulate gyrus area, and cingulum at the hippocampus area. White matter changes were investigated in terms of neurite density and orientation dispersion using the NODDI parameters ICVF and ODI. White matter changes were also measured in terms of the DTI parameters FA and MD. It was hypothesized that in older adults, changes in neurite density and orientation dispersion are associated with changes in performance of executive functions. It was also hypothesized that changes in FA and MD are associated with changes in performance of executive functions in older adults. In particular, it was expected that a decline in FA and an increase in MD are associated with a decline in executive function. Furthermore, this study also investigated the association between brain state and changes in measures of executive functions in healthy ageing. To test this relationship, NODDI and DTI parameters and executive functions were analysed at two timepoints. It was hypothesized that changes in FA, MD, and neurite density, and orientation dispersion are associated with changes in executive functions over time.

2 Materials and Methods

All data used in both studies came from the 1000BRAINS study (Caspers et al., 2014), a longitudinal population-based study focusing on brain structural and functional variability in

ageing. In both studies, the data analyzed have undergone the same pipeline described in the subsequent sections below.

MRI contraindications and previous neurosurgery are the exclusion criteria used in the 1000BRAINS study. These are described in detail by Caspers and colleagues (2014). Inclusion and exclusion criteria for each study are described accordingly in the respective sections on participants characteristics (Sections 2.7.1 and 2.8.1), including the total number of participants and the number of excluded participants. Participants in each study were selected separately based on the inclusion and exclusion criteria in each study. All participants gave written informed consent in accordance with the Declaration of Helsinki. Ethical approval (Ethics Vote numbers 11-4678 and 12-5199-BO) was given by the Ethics Committee of the University of Essen, Germany.

2.1 Data acquisition and pre-processing

The MRI scans were carried out at Forschungszentrum Jülich, Germany on a single MR scanner (3 Tesla Tim-TRIO, Siemens Medical Systems, Erlangen, Germany). Full scanning protocol is described in Caspers et al., 2014. Diffusion-weighted sequences were acquired in 30 directions (EPI, TR = 7.8 s, TE = 83 ms, 4 b0-images (interleaved), 30 images with b = 1000 s/mm^2, voxel resolution = 2 × 2 × 2 mm^3), 60 directions (EPI, TR = 6.3 s, TE = 81 ms, 7 b0-images (interleaved), 60 images with b = 1000 s/mm^2, voxel resolution = 2.4 × 2.4 × 2.4 mm^3), and 120 directions (EPI, TR = 8 s, TE = 112 ms, 13 b0-images (interleaved), 120 images with b = 2700 s/mm^2, voxel resolution = 2.4 × 2.4 × 2.4 mm^3). The diffusion-weighted images used in these analyses were in 60 and 120 directions, resampled to 1.25 × 1.25 × 1.25 mm^3. The b0-images were aligned to anatomical T1-weighted images acquired as 3D-MPRAGE (176 slices, TR = 2.25 s, TE = 3.03 ms, TI = 900 ms, FoV = 256 × 256 mm2, flip angle = 9◦, voxel resolution = 1 × 1 × 1 mm^3).

Motion correction on the diffusion images was implemented using FMRIB's Software Library (FSL) tool, eddy, (Andersson et al., 2016). Masks were created by combining the grey matter, white matter, and CSF tissue probability maps computed with Computational Anatomy Toolbox 12v5 (Gaser et al., 2024). The transformation mapping coordinates from T1-weighted space to diffusion MRI-space were then used to map the combined tissue probability images from T1-weighted space to diffusion MRI-space.

2.2 Diffusion data quality control

Automated tools were used for quality control of the diffusion MRI data based on the eddy output. In particular, the QUality Assessment for DMRI (QUAD) and the Study-wise QUality Assessment for DMRI (SQUAD; Bastiani et al., 2019) were applied separately on the b=1000 and b=2700 volumes. First, the following metrics were used in QUAD for quality control of each of the single subjects' diffusion images: volume-to-volume motion, within-volume motion, eddy current-induced distortions, susceptibility-induced distortions, outlier replacement, as well as SNR and contrast-to-noise ratio (CNR). Second, SQUAD was implemented for the group quality control using individual QUAD results and generated summary statistics of the metrics. The recommended summary metric for overall individual data quality is the qc_cnr value, which is one of the outputs from SQUAD. This is because it contains the averaged b0 SNR and diffusion CNR which quantifies the results of the pre-processing with FSL eddy. The qc_cnr values were then converted to z-scores and the average was computed to be subsequently used as the summary metric for overall individual data quality. Six participants had qc_cnr values that are 2 standard deviations from the group mean and were excluded from the analyses. One subject had a qc_cnr value of less than 2 standard deviations from the group mean but more than 2 standard deviations from the group mean in all other metrics. After visual inspection, this subject was also excluded.

2.3 Data parameter extraction

Extraction of NODDI parameters was done using the Microstructure Diffusion Toolbox version 0.20.0. As diffusion was modeled as a tensor, tensor fitting at each voxel was done with FSL Diffusion Toolbox component programme dtifit. In order to run the diffusion MRI data in the Diffusion Tensor Imaging ToolKit (DTI-TK; Zhang et al., 2006; Zhang et al., 2007) pipeline, the tensors were converted to DTI-TK compatible format using fsl_to_dtitk.

Extraction of FA and MD parameters were incorporated in the DTI-TK pipeline after registration and spatial normalisation pipeline described in Timmers et al., 2016. The DTI-TK pipeline is described in the following section.

2.4 Registration and spatial normalisation

To generate the study-specific template, registration and spatial normalisation of the diffusion tensor imaging (DTI) volumes were conducted using the DTI-TK pipeline. This pipeline is a tensor-based, group-wise registration recommended to improve the accuracy of the resulting study-specific template (Bach et al., 2014). Unlike the standard Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) registration pipeline which uses scalar information

only, the DTI-TK pipeline uses full-tensor information. Improved accuracy of the study-derived template is achieved by the inclusion of fibre orientations when aligning the individual white matter tracts (Keihaninejad et al., 2013). Furthermore, this template contained both the DTI data from the first visit and the second visit to avoid bias towards a specific time point. This means that each participant's data from the first and second timepoints were included in the study-specific template.

Using the DTI-TK pipeline, all diffusion images from the participants were iteratively registered and subsequently averaged. The first linear iteration was a rigid alignment (6 DOFs) to the initial template, the IXI ageing template, which has been optimized for use in this pipeline (Zhang et al., 2010). The second linear iteration was the affine alignment (12 DOFs) which further refined the study-specific template.

The NODDI data were registered to the study-specific template according to the procedure described in Timmers and colleagues (2016). First, the origin of the NODDI maps were set to zero using the DTI-TK tool SVAdjustVoxelspace. Second, these maps were resampled using the DTI-TK tool SVResample. Third, these maps were warped to the study-derived template using the DTI-TK tool deformationScalarVolume. Fourth, the combined transformation field was then computed and the data warped with this single transformation (Timmers et al. 2016). This resulted in isotropic diffusion images with $1mm^3$ resolution. These images were then averaged using the DTI-TK tool TVMean to derive the study-specific template.

Individual FA maps and a 4-D mean FA map were created using the DTI-TK tool TVtool.

2.5 Post-registration quality control

The TBSS script tbss_1_preproc was employed as part of image quality control of each participant's FA map as well as the mean FA map. This removed potential voxel outliers from the tensor fitting. Sample images of each participant's FA map were created using slicesdir. These images are in sagittal, coronal, and axial views. With the mean FA map overlaid on each participant's images, visual inspection of these images was conducted to ensure that the main white matter tracts were present and that no obvious artefacts were visible.

2.6 Skeletonisation of FA maps

All FA maps were merged after quality control. The TBSS script tbss_skeleton was used to generate the mean FA skeleton. This was then viewed in FSLeyes (Smith et al., 2004) to determine the threshold that gives the best alignment of the skeleton and the white matter tracts.

This entailed excluding skeletons extending towards the cortical surface where high inter-individual variability exists. The recommended threshold value is 0.2 according to the TBSS user guide and this was found suitable for this study. With this threshold value, the TBSS script tbss_4_prestats was used to create the binary skeleton mask of the mean FA map, the distance map for projection of FA data to the skeleton, and the 4D file containing the skeletonised FA data of all participants. The FA skeleton and distance map were used to skeletonise the MD and NODDI maps with the TBSS script tbss_non_FA.

2.7 Study 1: Ageing effects on white matter tracts measured by diffusion MRI parameters

2.7.1 Participants

Inclusion criteria were based on the availability of longitudinal diffusion MRI data in 60 and 120 directions at each of the 2 timepoints. Among the participants initially included (*N* = 419), 7 were excluded due to poor image quality, assessed during quality control described in Section 2.2. A further 13 participants were excluded after image quality control post-registration. A final sample of 399 participants comprised of 18 to 84 years old (mean age at first visit: 61.8 years (SD: 11.7), median age: 63.4 years (SD: 11.7); 173 females, 226 males). Within this sample, data analyses were also conducted on participants aged 55 years and above at the first timepoint (*N* = 322, mean age at first visit: 66.4 years (SD: 6.5), median age: 65.3 years (SD: 6.5); 140 females, 182 males). Average time interval between visits was 3.6 years, ranging from 1.7 to 5.8 years.

2.7.2 Diffusion MRI Data

Data acquisition, pre-processing, registration and spatial normalisation, post-registration quality control, and skeletonisation of diffusion MRI data used in this study were described in previous sections above (see sections 2.1 to 2.6).

For the longitudinal analyses, annual difference maps were created by splitting the skeletonised 4D file into respective time points (i.e., time point 1 and time point 2). This was done using the FSL tool fslsplit. The respective second visit maps were then subtracted from the first visit maps and then divided by the time interval between the two visits. The resulting individual annual difference maps of each participant were then merged to create one 4D annual difference map. This process was applied to each DTI and NODDI parameter.

For the cross-sectional analyses, maps from each time point were analyzed separately. These were obtained by splitting the skeletonised 4D file as described above.

2.7.3 Tract Extraction

This study focused on major projection and association fibre tracts, specifically the superior corona radiata, anterior corona radiata, posterior corona radiata, anterior limb of the internal capsule, posterior limb of the internal capsule, superior longitudinal fasciculus, posterior thalamic radiation, sagittal stratum, uncinate fasciculus, cingulum at the cingulate gyrus area, and cingulum at the hippocampus area. To extract these tracts in the right and left hemispheres, the JHU ICBM-DTI-81 (Mori et al., 2008) white matter labels distributed with FSL were propagated to the study-derived template space using the NiftyReg Segmentation Propagation (Modat et al., 2010). Binary masks of the tract labels were created and inspected to ensure that the masks fit the tracts. Small holes within the masks were manually filled. These masks were dilated and then used to extract the tract skeletons from the skeletonised 4D file. The FSL tool fslmeants was used to extract the mean values of each diffusion parameter in each tract skeleton.

2.7.4 Statistical Analyses

Statistical analyses were conducted on IBM SPSS Statistics version 24. The relationship between age and each diffusion measure on the tracts of interest was tested using a one-tailed non-parametric partial correlation (Spearman rho rank correlation). Control variables were sex and handedness based on the Edinburgh Handedness Inventory (Oldfield, 1971). Furthermore, Yendiki and colleagues (2014) found that head movement during scanning can impact results. Thus, head motion was controlled for using the eddy output that estimates how much the participant moved during MR scanning. Head motion relative to the first volume and head motion relative to the previous volume were reduced to one variable using principal component analysis. Post-hoc correction for multiple comparisons was done using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995) for decreasing the false discovery rate.

2.8 Study 2: Changes in executive functions in older age

2.8.1 Participants

The participants in this study were older adults (aged 55 years and above) from the 1000BRAINS cohort. Inclusion criteria were the availability of longitudinal data from 2 visits and a score above 8 in the DemTect (Kalbe et al., 2004). Specifically, participants were included if they had diffusion data in both 60 and 120 directions for the first and second visit ($N = 313$). Participants with missing scores on any of the neuropsychological tests described in Section 2.8.3 ($N = 18$) were excluded from the analyses, resulting in a final sample of 295 participants

(mean age at visit one: 66.28 years (SD: 6.43); 127 females, 170 males). The average interval between the two visits was 3.74 years (range: 1.75 - 5.83 years).

2.8.2 Diffusion MRI Data

Data acquisition, pre-processing, registration and spatial normalisation, post-registration quality control, and skeletonisation of diffusion MRI data used in this study were described in previous sections above. A study-derived template was created according to the procedure described in Section 2.4.

2.8.3 Neuropsychological Tests

To test for executive functions, scores on four tests were used. These tests were the Leistungs-Prüfungssystem 50+ Subtest 3 (Sturm et al., 1993), which measures reasoning and problem solving, the Farb-Wort-Interferenz Test (Jülich version), similar to the Stroop Test (Bäumler and Stroop, 1985; Stroop, 1935) which measures inhibition and susceptibility to interference, the Fünf-Punkte-Test (Jülich version), similar to the Five-Point Test (Regard et al., 1982) which measures figural fluency, and the Trail-Making Test (taken from CERAD-Plus; Morris et al., 1989) which measures attention and visual-motor speed, processing speed (Trail A), cognitive flexibility, executive function (Trail B), and concept shifting (B-A).

Test scores were converted to z-scores and then reduced to one composite score using principal component analysis (PCA) as a variable reduction approach. A Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy test statistic was obtained to test the suitability of the data for PCA. Scores at first visit yielded a KMO value of 0.67. Scores at second visit yielded a KMO value of 0.70. Both values exceeded the minimum KMO value of 0.6, indicating that the data were suitable for PCA (Kaiser, 1974). To derive the longitudinal test scores, component scores at second visit were subtracted from component scores at first visit divided by the number of years between visits. This resulted in annual difference test scores.

2.8.4 Statistical Analyses

IBM SPSS Statistics version 24 was used to calculate the z-scores of the neuropsychological tests as well as to conduct the PCA.

To test the relationship of white matter changes and changes in executive functions, each of the 4 diffusion parameters (i.e., FA, MD, ICVF, and ODI) was correlated with the executive functions score. Furthermore, to test the relationship between brain state and changes in executive functions in healthy ageing, each of the DTI and NODDI parameters at baseline were correlated with annual difference scores of executive functions. All correlations were

performed using voxel-wise analyses of the skeletonised diffusion MRI data. This was a permutation-based, voxel-wise nonparametric testing using the FSL tool randomise (Winkler et al., 2014). A total of 10,000 permutations were performed to reduce the margin-of-error to below 10% of the nominal alpha. Threshold-Free Cluster Enhancement (TFCE) corrected p-value images were generated using TFCE (Smith and Nichols, 2009) optimized for TBSS. Significance threshold was set at $p < 0.05$.

Age and sex were controlled for as well as the level of education according to the International Standard Classification of Education. Based on findings from Yendiki and colleagues (2014), head motion was controlled for using the eddy output that estimates participant head motion during scanning. Using PCA, one head motion variable was derived from head motion relative to the first volume and head motion relative to the previous volume. Handedness, based on the Edinburgh Handedness Inventory (Oldfield, 1971), was also included as a control variable.

The MRI Atlas of Human White Matter (Oishi et al., 2010) was used as a reference for identifying tracts with significant voxels.

3 Results

3.1 Study 1: Ageing effects on white matter tracts

This section outlines the correlations between age and the diffusion MRI parameters (FA and MD) and the NODDI parameters (ICVF and ODI) in older adults aged 55 years and above and across the whole sample (18 to 84 years). Cross-sectional and longitudinal results are presented in subsequent subsections.

P-values of all the diffusion parameters are reported in Table 1 on the next page.

Table 1: P-values of all diffusion parameters

	Older Adults												Whole Sample (Young and Older Adults)											
	Cross-sectional 1st Visit				Cross-sectional 2nd Visit				Longitudinal				Cross-sectional 1st Visit				Cross-sectional 2nd Visit				Longitudinal			
Tract	**FA**	**MD**	**ICVF**	**ODI**	**FA**	**MD**	**ICVF**	**ODI**	**FA**	**MD**	**ICVF**	**ODI**	**FA**	**MD**	**ICVF**	**ODI**	**FA**	**MD**	**ICVF**	**ODI**	**FA**	**MD**	**ICVF**	**ODI**
ACR_L	0.129	0.132	0.405	0.492	0.204	0.442	0.25	0.16	0.175	**0.048***	0.392	0.335	**0****	**0****	**0****	0.146	**0****	**0****	**0****	0.177	0.102	0.183	**0.008***	**0.027***
ACR_R	0.334	0.104	0.47	0.337	0.471	0.49	0.214	0.114	0.201	0.138	0.235	0.258	**0****	**0****	**0****	0.187	**0****	**0****	**0****	0.118	**0.04***	0.21	**0.003***	**0.004***
AIC_L	**0.03***	**0.011***	0.396	0.416	0.284	0.279	0.192	0.23	**0.002***	**0.019***	0.403	0.366	**0.01***	**0****	**0.001***	**0.004***	**0.016***	**0****	**0.001***	**0.025***	**0.046***	0.468	**0.01***	0.066
AIC_R	0.154	**0.04***	0.452	0.442	0.248	0.172	0.17	0.21	0.197	0.156	0.219	0.284	**0.001***	**0****	**0.001***	**0.034***	**0****	**0****	**0****	**0.026***	**0.048***	0.468	**0.003***	**0.009***
CCG_L	0.234	0.101	0.393	0.397	0.229	0.193	0.124	0.155	0.396	0.357	0.234	0.269	**0****	**0.007***	**0.012***	0.305	**0****	**0.001***	**0.003***	0.372	0.173	0.167	0.083	0.151
CCG_R	0.307	**0.029***	0.411	0.379	0.361	0.273	0.183	0.162	0.108	0.09	0.401	0.152	**0.001***	**0****	**0.007***	0.38	**0.001***	**0****	**0.008***	0.347	0.109	0.125	**0.034***	0.11
SS_L	0.141	0.111	0.304	0.284	0.386	0.444	0.139	0.199	0.088	0.069	0.267	0.207	**0****	**0****	0.082	0.313	**0****	**0****	**0.012***	0.35	**0.005***	0.114	**0.027***	0.135
SS_R	0.131	0.296	0.498	0.391	0.231	0.465	0.164	0.284	0.181	0.393	0.353	0.4	**0****	**0****	0.053	0.393	**0****	**0****	**0.04***	0.223	**0.033***	**0.046***	**0.026***	0.152
CH_L	0.275	0.323	0.388	0.341	0.436	0.482	0.148	0.2	0.368	0.365	0.248	0.22	0.142	0.175	0.098	0.363	0.227	0.307	**0.032***	0.158	0.236	0.46	**0.025***	**0.047***
CH_R	0.357	0.236	0.487	0.294	0.422	0.415	0.192	0.281	0.49	0.494	0.368	0.219	0.107	0.13	0.068	0.464	**0.032***	0.301	0.077	0.479	**0.053***	0.466	0.051	0.16
PCR_L	0.073	**0.014***	0.415	0.477	0.271	0.183	0.16	0.165	0.093	**0.019***	0.412	0.455	**0****	**0****	**0.005***	0.239	**0****	**0****	**0.001***	0.15	0.443	**0.044***	**0.01***	**0.012***
PCR_R	0.079	**0.048***	0.376	0.374	0.114	0.075	0.169	0.312	0.297	0.427	0.475	0.421	**0****	**0****	**0.007***	0.379	**0****	**0****	**0.002***	0.356	0.199	0.081	**0.008***	**0.03***
PIC_L	0.117	**0.022***	0.464	0.475	0.351	0.499	0.137	0.122	**0.007***	0.06	0.339	0.29	**0.029***	**0****	**0.023***	0.058	0.366	**0.002***	**0.011***	**0.047***	0.49	0.406	**0.012***	**0.025***
PIC_R	**0.013***	**0.043***	0.494	0.293	**0.036***	0.086	0.091	0.212	0.5	0.472	0.16	0.248	**0****	**0****	**0.016***	0.246	**0****	**0****	**0.001***	0.093	0.296	0.16	**0.005***	**0.018***
PTR_L	0.149	0.31	0.421	0.211	0.158	0.425	0.216	0.407	0.329	0.476	0.281	0.454	**0****	**0****	**0.012***	0.164	**0****	**0****	**0.001***	0.198	**0****	**0.012***	**0.008***	0.055
PTR_R	**0.045***	0.335	0.285	0.15	**0.05***	0.214	0.179	0.25	0.461	0.168	0.444	0.378	**0****	**0****	**0.003***	0.136	**0****	**0****	**0.002***	**0.036***	**0.017***	**0.015***	**0.01***	0.121
SCR_L	0.269	0.06	0.408	0.478	0.475	0.251	0.127	0.093	0.121	**0.034***	0.338	0.297	**0****	**0****	**0****	**0.021***	**0.002***	**0****	**0****	**0.005***	0.48	0.449	**0.009***	**0.01***
SCR_R	0.161	0.119	0.485	0.381	0.409	0.395	0.185	0.142	0.38	0.064	0.262	0.249	**0****	**0****	**0****	**0.034***	**0.001***	**0****	**0****	**0.005***	0.263	0.483	**0.005***	**0.007***
SLF_L	0.078	**0.012***	0.446	0.406	0.222	0.272	0.262	0.196	0.086	**0.027***	0.383	0.285	**0****	**0****	**0.007***	0.47	**0****	**0****	**0.003***	0.318	0.063	0.42	**0.009***	**0.014***
SLF_R	**0.023***	**0.033***	0.41	0.294	0.103	0.263	0.212	0.242	0.285	0.104	0.378	0.236	**0****	**0****	**0.007***	0.358	**0****	**0****	**0.003***	0.4	**0.042***	0.346	**0.012***	**0.023***
UNC_L	0.281	0.178	0.355	0.288	0.423	0.259	0.306	0.226	0.389	0.357	0.237	0.253	0.39	**0.003***	0.141	0.369	0.352	**0.003***	0.095	0.172	0.082	0.45	**0.018***	**0.029***
UNC_R	0.262	**0.008***	0.438	0.486	0.366	0.063	0.107	0.094	0.312	0.228	0.191	0.098	0.209	**0.003***	**0.048***	**0.018***	0.306	**0.023***	**0.016***	**0.016***	0.215	0.139	**0.04***	0.077

P-values where alpha level is 0.05 and significant p-values ($p \leq 0.05$) are with asterisks. Highlighted values indicate significant adjusted p-value after correction for multiple comparisons using Benjamini and Hochberg false discovery rate. 0** indicates $p < 0.001$.

Key: FA, fractional anisotropy; MD, mean diffusivity; ICVF, intra-cellular volume fraction; ODI, orientation dispersion index; ACR_L, left anterior corona radiata; ACR_R, right anterior corona radiata; AIC_L, left anterior limb of the internal capsule AIC_R, right anterior limb of the internal capsule; CCG_L, left cingulum at the cingulate gyrus area; CCG_R, right cingulum at the cingulate gyrus area; CH_L, left cingulum (hippocampus area); CH_R, right cingulum (hippocampus area); PCR_L, left posterior corona radiata; PCR_R, right posterior corona radiata; PIC_L, left posterior limb of the internal capsule; PIC_R, right posterior limb of the internal capsule; PTR_L, left posterior thalamic radiation; PTR_R, right posterior thalamic radiation; SCR_L, left superior corona radiata; SCR_R, right superior corona radiata; SLF_L, left superior longitudinal fasciculus, SLF_R, right superior longitudinal fasciculus; SS_L, left sagittal stratum; SS_R, right sagittal stratum, UNC_L, left uncinate fasciculus; UNC_R, right uncinate fasciculus.

3.1.1 Cross-sectional and longitudinal correlations between age and FA

Cross-sectionally, the FA values in older adults at the first visit are similar among all participants, with a slight decreasing trend with increasing age as shown in Fig. 3a below for the left hemisphere tracts and the corresponding right hemisphere tracts in Fig. 3b. Specifically, among older adults aged 55 years and above, data from the first visit revealed a negative correlation ($p \leq 0.05$) between age and FA in the left anterior limb of the internal capsule, right posterior limb of the internal capsule, right posterior thalamic radiation, and right superior longitudinal fasciculus. Thus, older age significantly correlated with lower FA in these tracts.

Separate cross-sectional analyses were conducted on the whole sample of participants aged 18 to 84 years. Using data from the first visit, there was negative correlation between age and FA, indicating a decline in FA as age increases. These are shown in Fig. 3a for the left tracts and Fig. 3b for the right tracts. Similar results were obtained when data from the second visit were analysed and these are shown in Fig. 7 in the Appendix.

Cross-sectional analyses of data from the second visit of older adults showed no significant correlation between age and FA. An exception is the FA in the right posterior limb of the internal capsule and right posterior thalamic radiation which was negatively correlated with age. However, these associations did not hold after correcting for multiple comparisons, with p-values reported in Table 1 above. The FA values at second visit plotted against age can be seen in Fig. 7 in the Appendix.

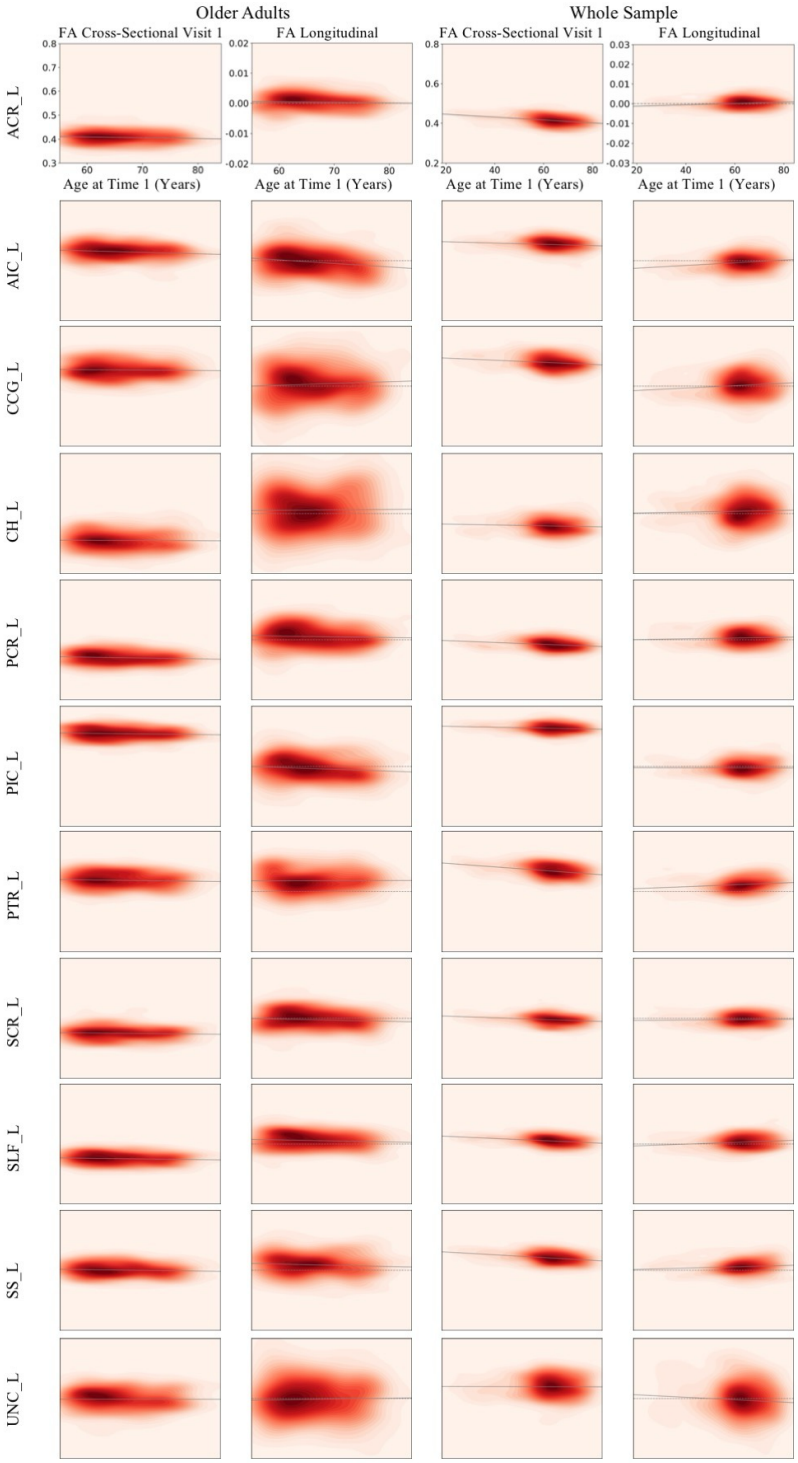

Fig. 3a: Cross-sectional and longitudinal tract mean FA diffusion values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show a greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_L, left anterior corona radiata; AIC_L, left anterior limb of the internal capsule; CCG_L, left cingulum at the cingulate gyrus area; CH_L, left cingulum at the hippocampus area; PCR_L, left posterior corona radiata; PIC_L, left posterior limb of the internal capsule; PTR_L, left posterior thalamic radiation; SCR_L, left superior corona radiata; SLF_L, left superior longitudinal fasciculus; SS_L, left sagittal stratum; UNC_L, left uncinate fasciculus.

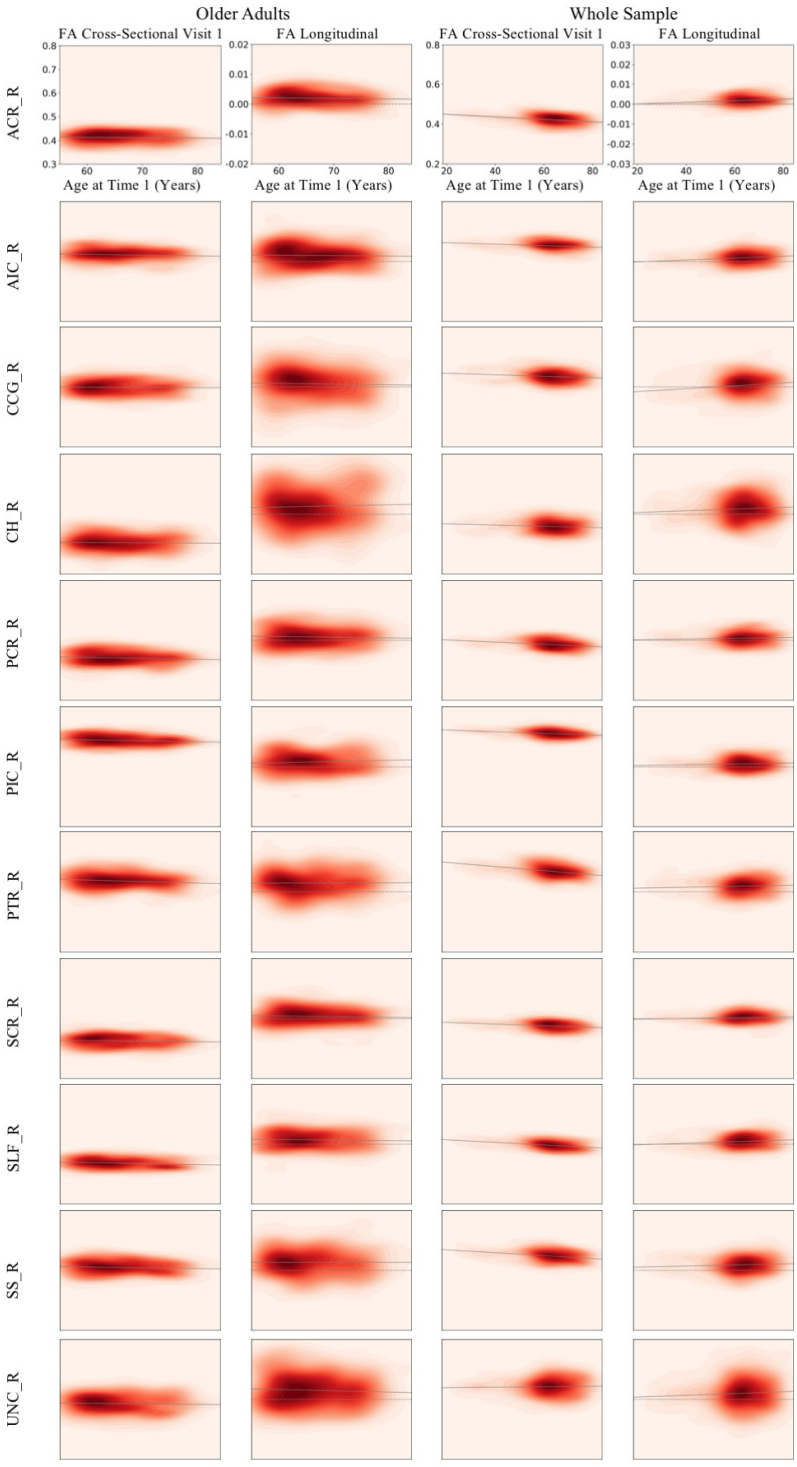

Fig. 3b: Cross-sectional and longitudinal tract mean FA diffusion values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_R, right anterior corona radiata; AIC_R, right anterior limb of the internal capsule; CCG_R, right cingulum at the cingulate gyrus area; CH_R, right cingulum at the hippocampus area; PCR_R, right posterior corona radiata; PIC_R, right posterior limb of the internal capsule; PTR_R, right posterior thalamic radiation; SCR_R, right superior corona radiata; SLF_R, right superior longitudinal fasciculus; SS_R, right sagittal stratum; UNC_R, right uncinate fasciculus.

Results of longitudinal analyses show that in older adults aged 55 and above at first visit, there was a negative correlation between age and changes in the diffusion parameters. Older age significantly correlated ($p \leq 0.05$) with smaller annual difference in FA in the left anterior limb of the internal capsule and the left posterior limb of the internal capsule. After correcting for multiple comparisons, only the association between age and FA annual difference in the left anterior limb of the internal capsule remained significant. Although no further subgroup analyses were conducted, it can be seen in Fig. 3a that participants around the age of 55 to 60 years had a small change in FA in the left anterior limb of the internal capsule. On the other hand, participants aged between 60 and 65 years showed no significant changes while participants aged from 65 years onwards have increased changes in FA.

In other association and projection tracts, longitudinal changes among older adults were not significant in this study. However, density plots (Fig. 3a above) show a trend of changes over time which is generally a smaller change in FA. Exceptions to this are the FA annual difference in the left posterior limb of the internal capsule and left superior corona radiata which showed a trend of no change to higher changes over time. Furthermore, FA annual difference in the left uncinate fasciculus showed a trend of increasing changes to no change in older age. These trends are not significantly different across the older participants.

In the density plots for annual difference in FA (Fig. 3a and Fig. 3b above) among older adults, regression lines above zero indicate a trend of decreasing FA over time although this is not significant. Exceptions to this are the left posterior limb of the internal capsule and left superior corona radiata where the regression lines ran from zero downwards, indicating a trend of no difference to higher FA over time. The regression line for FA annual difference in the left uncinate fasciculus ran from below zero to around zero, indicating higher FA over time but approaching no difference in older age. The density plots also show that the FA annual difference in all tracts is similar and not significantly different among older adults with the exception of the left anterior limb of the internal capsule.

Longitudinal analyses across the whole age range (18 to 84 years) showed that there were significant positive correlations ($p \leq 0.05$) between age and FA in a number of tracts. However, this effect remained only in the left posterior thalamic radiation after the Benjamini and Hochberg false discovery rate correction for multiple comparison where higher age correlated with higher annual difference in FA.

3.1.2 Cross-sectional and longitudinal correlations between age and MD

Among older adults, cross-sectional analyses from the first visit showed that there was a significant positive correlation ($p \leq 0.05$) between age and MD in the bilateral anterior limb

of the internal capsule, right cingulum (cingulate gyrus area), bilateral posterior corona radiata, bilateral posterior limb of the internal capsule, bilateral superior longitudinal fasciculus, and right uncinate fasciculus. Thus, as the age increased, the MD increased in these tracts. However, the associations between age and MD disappeared after correcting for multiple comparison using the Benjamini and Hochberg false discovery rate approach. However, there was a slight increasing trend in MD as age increases but it remains largely similar among the older adults as shown in Fig. 4a and Fig. 4b below. Cross-sectional analyses of data from the second visit of older adults showed no significant correlation between age and MD. These are shown in Fig. 8 in the Appendix.

In the cross-sectional analyses using data from the first visit of all participants aged 18 to 84 years, there was a positive correlation between age and MD. As age increased, MD also increased. These age effects were evident in all the tracts included in this study, with the exception of the left and right cingulum in the hippocampus area. These are shown in Fig. 4a and Fig. 4b below. These results were similar when data from the second visit were analysed. Density plots of the results from the second visit for both older adults and the whole sample are shown in Fig. 8 in the Appendix.

Fig. 4a: Cross-sectional and longitudinal tract mean MD diffusion values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_L, left anterior corona radiata; AIC_L, left anterior limb of the internal capsule; CCG_L, left cingulum at the cingulate gyrus area; CH_L, left cingulum at the hippocampus area; PCR_L, left posterior corona radiata; PIC_L, left posterior limb of the internal capsule; PTR_L, left posterior thalamic radiation; SCR_L, left superior corona radiata; SLF_L, left superior longitudinal fasciculus; SS_L, left sagittal stratum; UNC_L, left uncinate fasciculus.

Fig. 4b: Cross-sectional and longitudinal tract mean MD diffusion values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_R, right anterior corona radiata; AIC_R, right anterior limb of the internal capsule; CCG_R, right cingulum at the cingulate gyrus area; CH_R, right cingulum at the hippocampus area; PCR_R, right posterior corona radiata; PIC_R, right posterior limb of the internal capsule; PTR_R, right posterior thalamic radiation; SCR_R, right superior corona radiata; SLF_R, right superior longitudinal fasciculus; SS_R, right sagittal stratum; UNC_R, right uncinate fasciculus.

Longitudinal results showed that the annual difference in MD was positively correlated ($p \leq 0.05$) with age in older adults, indicating that MD increased as age increased. These effects were found in left hemispheric tracts particularly in the anterior corona radiata, anterior limb of the internal capsule, posterior corona radiata, superior corona radiata, and superior longitudinal fasciculus. However, after the Benjamini and Hochberg false discovery rate correction, the effects were no longer significant. These are illustrated in Fig. 4a and Fig. 4b.

Across the whole age range, there were no significant correlations between age and longitudinal change in MD across all the tracts studied. Nonetheless, density plots of MD (Fig. 4a and Fig. 4b) from across the whole age range show a trend of decreasing MD annual difference (i.e., approaching zero) with increasing age in some left hemisphere tracts (anterior corona radiata, anterior and posterior limb of the internal capsule, posterior and superior corona radiata, superior longitudinal fasciculus, superior longitudinal fasciculus and sagittal stratum and the right uncinate fasciculus) but remaining relatively flat in the other tracts indicative of no change over time. The regression line remains below zero indicating higher MD at the second visit although this change remained insignificant.

3.1.3 Cross-sectional and longitudinal correlations between age and ICVF

Among older adults, there were no significant correlations between age and ICVF in cross-sectional analyses of data from the first and second visits. The NODDI parameter ICVF remained similar for the older adult participants as shown in density plots of the first visit in Fig. 5a and Fig. 5b below. These values remained around zero and therefore stayed relatively stable over time. Density plots of the results from the second visit are shown in Fig. 9 in the Appendix.

Across the whole sample of participants aged 18 to 84 years, cross-sectional analysis of data from the first visit showed that there was a negative correlation between age and ICVF. As age increased, ICVF decreased. Cross-sectional data from the second visit also showed a negative correlation between age and ICVF across the whole age range. The p-values are shown in Table 1. Density plots of the results from the second visit for the whole sample are shown in Fig. 9 in the Appendix.

Longitudinal results of the older adults showed that ICVF values were similar and remain stable over time across the whole age range as illustrated in Fig. 5a and 5b. This indicates that with increasing age, ICVF changes are not significant. However, across the whole age range, negative correlation ($p \leq 0.05$) between age and ICVF annual difference remained

significant after correcting for multiple comparison. This relationship was found in all major association and projection tracts.

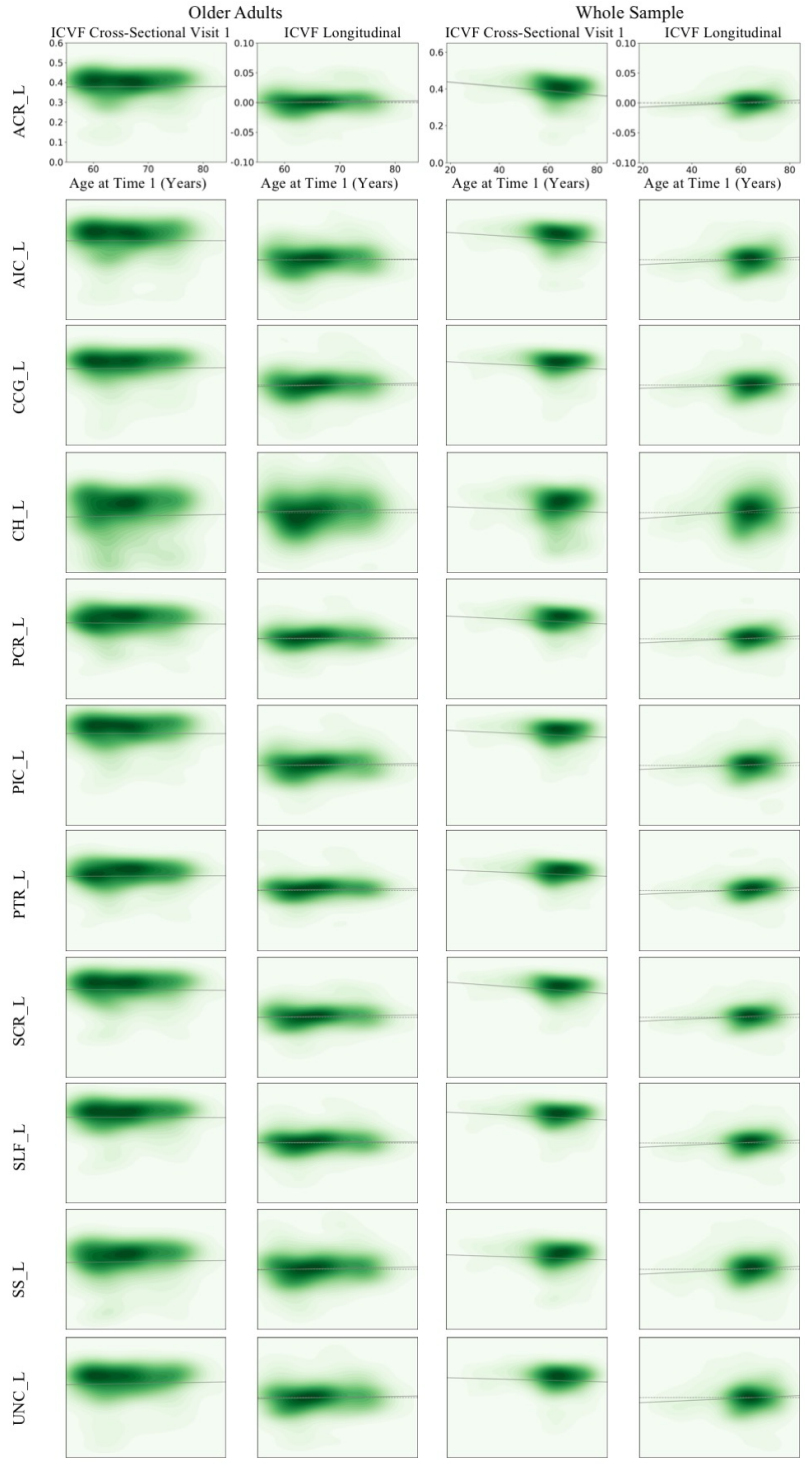

Fig. 5a: Cross-sectional and longitudinal tract mean ICVF diffusion plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_L, left anterior corona radiata; AIC_L, left anterior limb of the internal capsule; CCG_L, left cingulum at the cingulate gyrus area; CH_L, left cingulum at the hippocampus area; PCR_L, left posterior corona radiata; PIC_L, left posterior limb of the internal capsule; PTR_L, left posterior thalamic radiation; SCR_L, left superior corona radiata; SLF_L, left superior longitudinal fasciculus; SS_L, left sagittal stratum; UNC_L, left uncinate fasciculus.

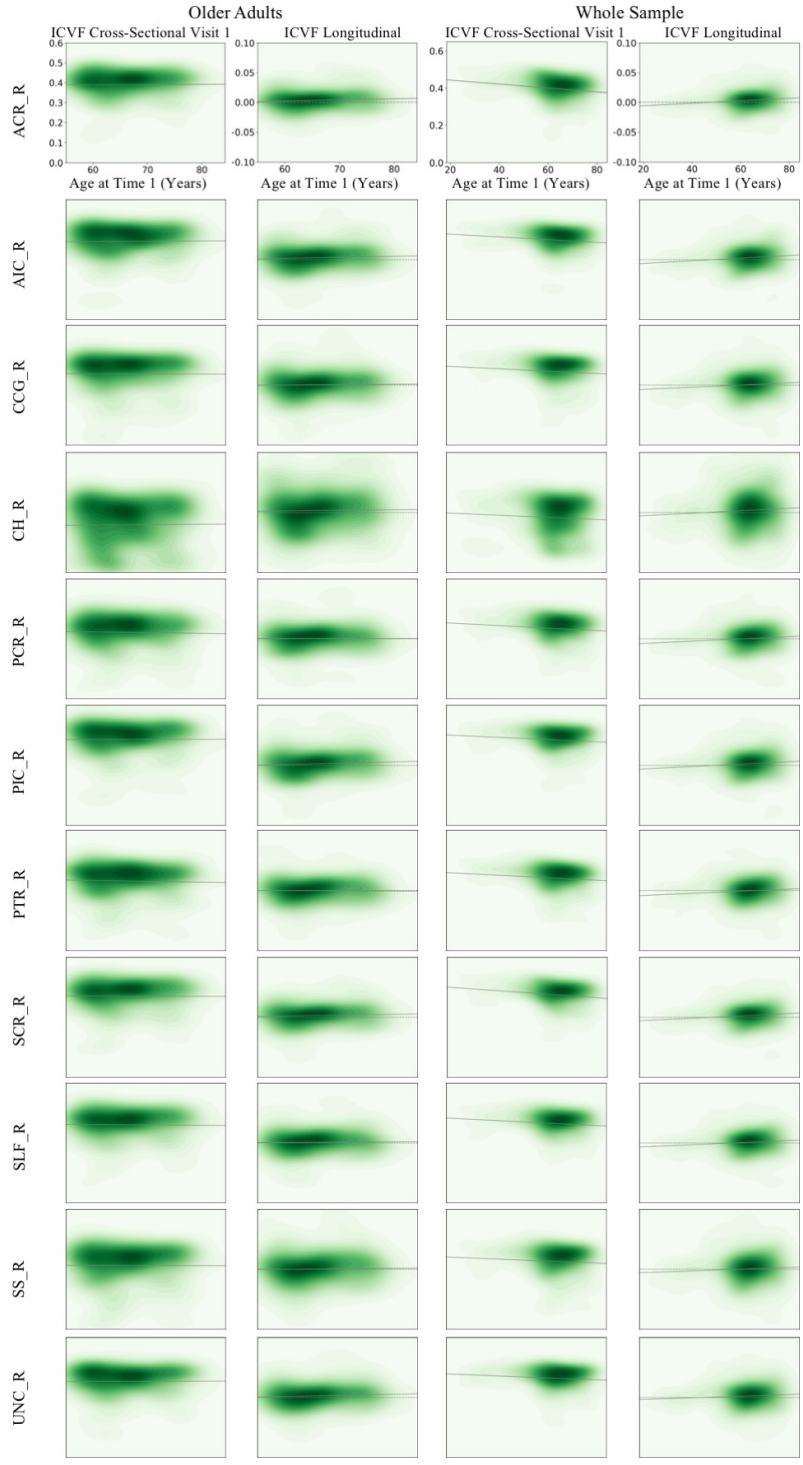

Fig. 5b: Cross-sectional and longitudinal tract mean ICVF values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_R, right anterior corona radiata; AIC_R, right anterior limb of the internal capsule; CCG_R, right cingulum at the cingulate gyrus area; CH_R, right cingulum at the hippocampus area; PCR_R, right posterior corona radiata; PIC_R, right posterior limb of the internal capsule; PTR_R, right posterior thalamic radiation; SCR_R, right superior corona radiata; SLF_R, right superior longitudinal fasciculus; SS_R, right sagittal stratum; UNC_R, right uncinate fasciculus.

3.1.4 Cross-sectional and longitudinal correlations between age and ODI

Density plots of ODI (Fig. 6a and Fig. 6b) show that these parameters are similar cross-sectionally among older adults. Analyses of cross-sectional data from the second visit of older adults yielded similar results. Across the whole sample, cross-sectional data using the first visit showed no significant correlations between age and ODI as shown in Fig. 6a and Fig. 6b. Analyses of data from the second visit also yielded similar results. Density plots of the results from the second visit for both older adults and the whole sample are shown in Fig. 10 in the Appendix.

Among older adults, longitudinal results show that it remains around zero and therefore staying relatively stable over time. In terms of annual difference in ODI across the whole age range, no significant correlations with age remained after correction. These are illustrated in Fig. 6a and Fig. 6b.

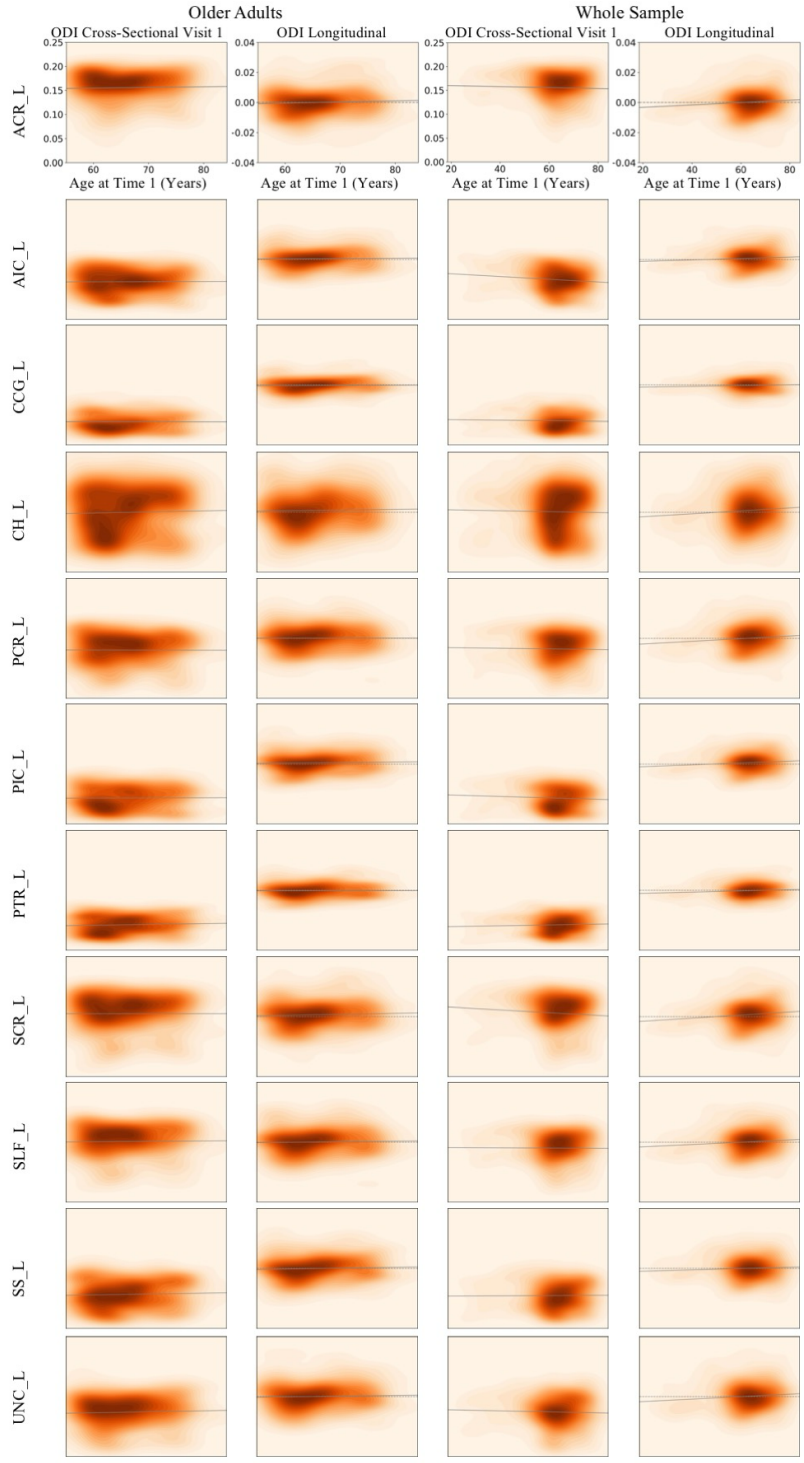

Fig. 6a: Cross-sectional and longitudinal tract mean ODI values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_L, left anterior corona radiata; AIC_L, left anterior limb of the internal capsule; CCG_L, left cingulum at the cingulate gyrus area; CH_L, left cingulum at the hippocampus area; PCR_L, left posterior corona radiata; PIC_L, left posterior limb of the internal capsule; PTR_L, left posterior thalamic radiation; SCR_L, left superior corona radiata; SLF_L, left superior longitudinal fasciculus; SS_L, left sagittal stratum; UNC_L, left uncinate fasciculus.

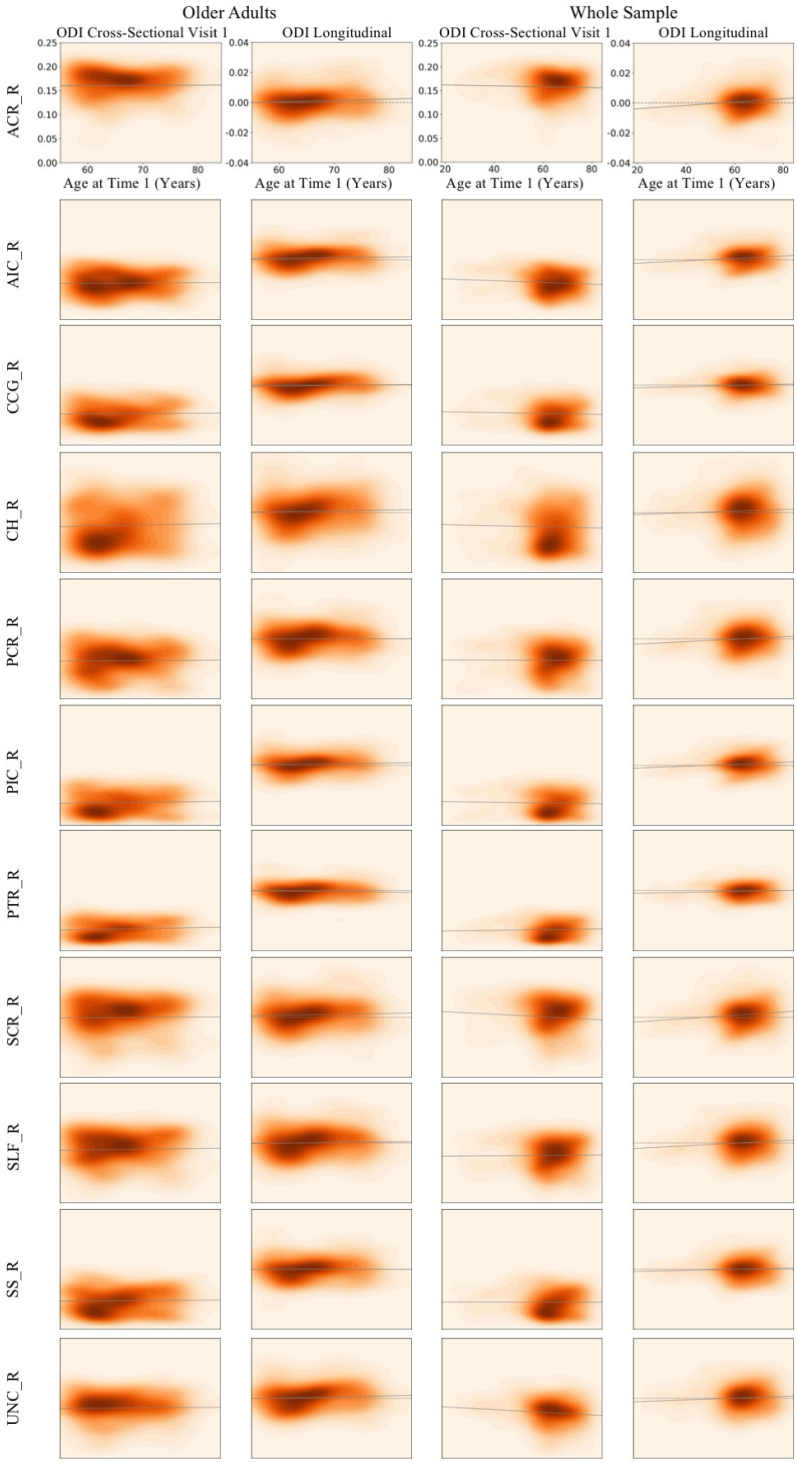

Fig. 6b: Cross-sectional and longitudinal tract mean ODI values plotted against age in older adults and in young to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero on the y-axis of longitudinal plots. Key: ACR_R, right anterior corona radiata; AIC_R, right anterior limb of the internal capsule; CCG_R, right cingulum at the cingulate gyrus area; CH_R, right cingulum at the hippocampus area; PCR_R, right posterior corona radiata; PIC_R, right posterior limb of the internal capsule; PTR_R, right posterior thalamic radiation; SCR_R, right superior corona radiata; SLF_R, right superior longitudinal fasciculus; SS_R, right sagittal stratum; UNC_R, right uncinate fasciculus.

3.2 Study 2: Changes in executive functions in older age

3.2.1 Neuropsychological tests

Descriptive statistics (i.e., z-scores means, standard deviations, and range) for the four neuropsychological tests of executive functions are summarized in Table 2 below.

One component was extracted from the PCA resulting in one composite z-score of executive functions. These scores from the first and second visit can be found in Tables 3 and 4 respectively.

Table 2: Executive function tests included in the analyses and summary statistics of group performance

Name of test	Task	Scoring	Raw Mean (±SD)		Z-scores Range	
			Visit 1	Visit 2	Visit 1	Visit 2
Leistungs - Prüfungssystem 50+, Subtest 3 (Sturm et al., 1993)	Identify and cross out irregularities in rows of geometric figures within 5 minutes	Total number of correct answers	21.76 (4.67)	21.82 (5.51)	-2.94 - 2.62	-2.51 - 2.75
Farb-Wort- Interferenz-Test (Jülich version similar to the Stroop Test, Stroop, 1935; Bäumler and Stroop, 1985)	1. Reading (FWL) color-words 2. Naming (FSB) colors 3. Naming the color of the letters of the color word	Time difference (sec.) between naming the color of the letters (part 3) and reading color words (part 2)	41.76(23.87)	40.60 (22.06)	-1.60 - 11.10	-1.96 - 9.36
Fünf-PunkteTest (Jülich version; similar to Regard et al., 1982)	Produce unique designs by connecting five dots within each rectangle within 3 minutes.	Total number of unique patterns of design	27.57(7.30)	26.42 (6.72)	-2.40 - 3.34	-2.15 - 3.36
Trail-Making-Test (taken from CERAD-Plus; Morris et al., 1989)	Part A: Connecting numbers in ascending order Part B: Alternately connecting numbers and letters in ascending order	Time difference (sec.) between Part B and Part A	49.03 (36.66)	50.22 (30.94)	-1.29 - 7.42	-1.48 - 5.13

Table 3: Principal Components Analysis for the neuropsychological tests z scores at first visit: Eigenvalues before and after extraction and percentage of variance explained before and after extraction

Component	Total	Initial Eigenvalues		Extraction Sums of Squared Loadings		
		% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1 (zLPS1)	2.189	54.718	54.718	2.189	54.718	54.718
2 (zFWT1)	0.888	22.190	76.907			
3 (zFPT1)	0.493	12.318	89.225			
4 (zTMT1)	0.431	10.775	100.000			

Key: zLPS1, z score of Leistungs - Prüfungssystem 50+ (Subtest 3) at first visit; zFWT1, z score of Farb-Wort- Interferenz-Test at first visit; zFPT1, z score of Fünf-PunkteTest at first visit; zTMT1, z score of Trail-Making-Test at first visit.

Table 4: Results of the Principal Components Analysis for the neuropsychological tests z scores at second visit: Eigenvalues before and after extraction and percentage of variance explained before and after extraction

Component	Total	Initial Eigenvalues		Extraction Sums of Squared Loadings		
		% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1 (zLPS2)	2.155	53.882	53.882	2.155	53.882	53.882
2 (zFWT2)	0.761	19.020	72.902			
3 (zFPT2)	0.665	16.624	89.526			
4 (zTMT2)	0.419	10.474	100.000			

Key: zLPS2, z score of Leistungs - Prüfungssystem 50+ (Subtest 3) at second visit; zFWT2, z score of Farb-Wort- Interferenz-Test at second visit; zFPT2, z score of Fünf-PunkteTest at second visit; zTMT2, z score of Trail-Making-Test at second visit.

3.2.2 Longitudinal correlations between executive functions and diffusion parameters

There was a negative correlation ($p > 0.05$) between changes in MD and changes in executive functions reduced to one component. Thus, greater changes in MD were associated with less changes in executive functions while less change in MD was associated with greater changes in executive functions. Although the directionality of these changes was not tested, raw individual data show that these changes were bidirectional, both positive and negative. These were observed specifically in the left anterior and posterior limb of the internal capsule, retrolenticular part of the internal capsule, parts of the sagittal stratum, parts of the posterior thalamic radiation, and tracts extending towards the temporal gyrus area as shown in Fig. 11 A-E.

No significant associations were found between changes in executive functions and changes in FA, ICVF, and ODI.

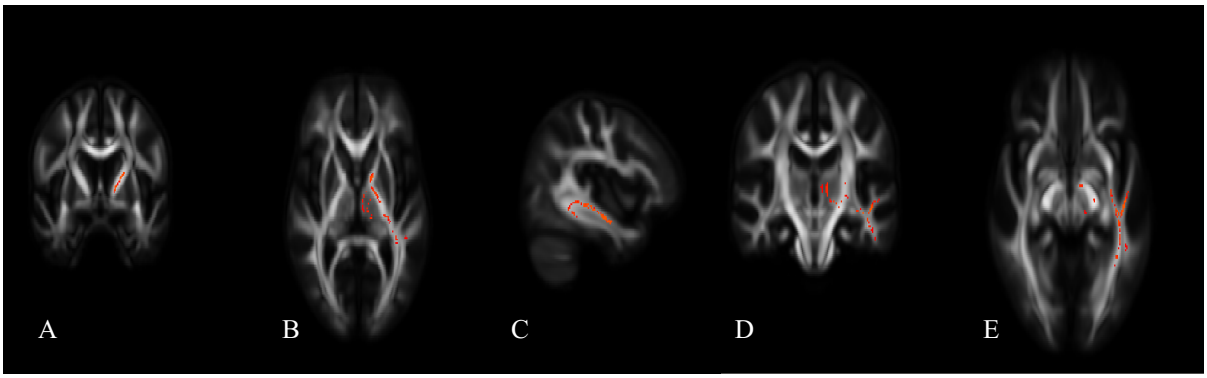

Fig. 11: Coronal, axial, and sagittal views of significant voxels ($p < 0.05$). Changes in executive functions negatively associated with changes in the left anterior, posterior, and retrolenticular part of the internal capsule (A and B), parts of the left sagittal stratum (C and E), parts of the left posterior thalamic radiation (C), left temporal gyrus (C, D, E).

3.2.3 Correlations between brain state and changes in measures of executive functions

Baseline MD positively correlated with longitudinal changes in executive functions ($p < 0.05$). Therefore, lower MD at baseline was associated with less change in executive functions over time while higher MD at baseline was associated with greater change in executive functions. This bilateral effect was observed in the superior longitudinal fasciculus, anterior, superior, and posterior corona radiata, the external and internal capsule, and white matter tracts on the gyri such as the superior frontal gyrus, pre- and post-central gyri. This was also observed

in the genu, body, and splenium of the corpus callosum. Fig. 12 A-F illustrate this significant association in the above-mentioned tracts.

There were no significant correlations between FA at baseline and longitudinal changes in executive functions. There were also no significant correlations between either of the NODDI parameters (ICVF and ODI) and changes in executive functions over time.

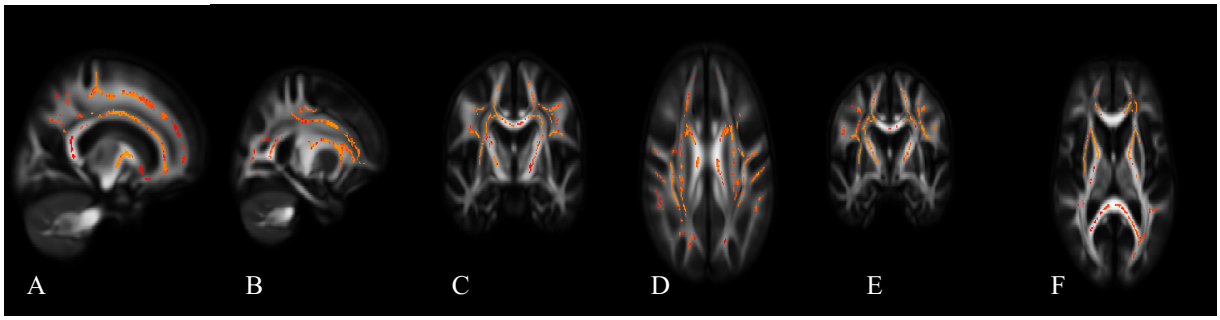

Fig. 12: Coronal, axial, and sagittal views of significant voxels ($p < 0.05$). Brain state at Timepoint 1 (Baseline) correlate positively with changes in executive functions. These effects are evident in the genu(A), body (A, D), and splenium of the corpus callosum (A, D), anterior corona radiata, superior corona radiata, and posterior corona radiata (A, B, D), superior longitudinal fasciculus (D), external capsule (F) and internal capsule (A), and white matter tracts on the superior frontal gyrus, pre- and post-central gyrus (D, E).

4 Discussion and Conclusions

4.1 Ageing effects on white matter tracts measured by diffusion MRI parameters

The first study aimed to investigate white matter changes that occur as part of the normal ageing process. These were examined in a population-based cohort of community-dwelling adults. Specifically, longitudinal white matter changes and cross-sectional differences were analyzed across a sample of young to older adults and in a separate sub-sample comprised of older adults aged 55 years and above. Parameters from the NODDI model (ICVF and ODI) as well as from the diffusion tensor model (FA and MD) were used as indicators of white matter changes.

Intra-individual white matter changes in young to older adults, as reflected in the results of the longitudinal analyses, were significant only in the left posterior thalamic radiation in terms of FA. There were no significant changes in MD in any of the tracts studied. Smaller longitudinal studies have also reported no change in FA and MD in healthy adults (Sullivan et al., 2010a) and in healthy controls (Blain et al., 2007; Sidaros et al., 2008). Taken together, these results and the current study results indicate that in the absence of disease, FA and MD

do not significantly change annually within a 3-year-average interval. Thus, cross-sectional differences observed in young to older adults likely reflect an overestimation of age effects and the significant positive age effect observed on the left posterior thalamic radiation could potentially be due to chance.

Longitudinal changes were also studied among older adults aged between 55 and 84 years. Longitudinal analyses showed no significant intra-individual white matter changes among older adults in terms of FA and MD. This is consistent with a previous longitudinal study on older adults aged 59 to 85 years which showed no significant change on annual total or regional brain volumes, including white matter volume (Resnick et al., 2000). Similarly, there was also no significant change at a 2-year-interval (Sullivan et al., 2010a) and at an 8-month-interval (Blain et al., 2007). Given that in normal ageing, neuronal loss may be less than previously expected (Morrison & Hof, 1997), it is reasonable to believe that neurite loss is also small in normal ageing and does not impact greatly on white matter changes, particularly in old age. It is also possible that the inter-individual variability among older adults is also high and therefore a mean age effect was not observed. Indeed, studies have shown that inter-individual variability increases in older age (for review see Christensen, 2001). In contrast to previous longitudinal ageing studies (e.g., Coelho et al., 2021; Sexton et al., 2014) where FA decreased and MD increased over time, the current study revealed heterogeneous increase and decrease in these parameters. This variability suggests that white matter changes measured in FA and MD are potentially influenced by factors other than age. For example, lifestyle could possibly explain the variability among older adults. Evidence suggests that lifestyle factors such as cardiorespiratory fitness have a positive impact on white matter structure in older age (Hayes et al., 2015). Furthermore, there is evidence that genetics and early-life influences on brain structure contribute to this variability (Vidal-Pineiro et al., 2021).

In contrast to longitudinal findings, cross-sectional ageing effects measured by FA and MD were evident in major projection and association tracts in young to older adults. A decrease in FA and an increase in MD were observed as age increased. These results are consistent with previous findings in other cross-sectional studies (e.g., Lebel et al., 2012; Salat et al., 2005) and are generally interpreted as deterioration of white matter tracts in ageing. Nevertheless, given that cross-sectional studies provide only one measurement from each participant, it is not possible to conclude that this is an indication of change within an individual in ageing. Furthermore, a decline in FA and increase in MD within an individual are not necessarily an indication of decline in white matter. It has been reported that majority of the voxels and fixels within a voxel contain crossing or kissing fibres which are particularly highest in the posterior part of the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, middle

longitudinal fasciculus, parieto-thalamic and occipito-thalamic optic radiations connections, parieto-striatal and parieto-occipital pontine tract (Schilling et al., 2022). In these areas, an increase in FA may be observed despite white matter degradation as fibres become more aligned due to some loss of crossing or kissing fibres. It is possible then that cross-sectional age effects are overestimated. This is in contrast to a previous finding that age effects are greater in longitudinal observations than in cross-sectional observations (Barrick et al., 2010). It is important to note, however, that in the study by Barrick and colleagues (2010), the observed ageing effects may have been due to the sample characteristics (i.e., a small sample ($N = 73$) of 50 to 92 years and true ageing effects may have been overestimated longitudinally.

Cross-sectional analyses of white matter changes were also conducted on adults aged 55 years and above on the first visit. Cross-sectionally, there were no significant differences in FA and MD. This is in contrast to the observed cross-sectional differences in FA and MD when younger adults are included in the analyses. Our results are also in contrast to another cross-sectional study by Cox and colleagues (2016) on UK Biobank participants where ageing effects were observed. However, the UK Biobank participants were younger (44 – 77 years old) compared to the older adults in this study (55- 84 years old) and the DTI parameters were derived from tractography. The different methodological approach might have contributed to the difference in results. Kuchling and colleagues (2018) have demonstrated that in TBSS-based and probabilistic tractography-based analyses, different FA values can be obtained between the two methods.

Given that DTI parameters are non-specific and cannot distinguish which factors contribute to the changes in these parameters, analyses went beyond DTI parameters FA and MD to better capture the complexity of white matter changes. By studying the NODDI parameters ICVF and ODI, changes were explored specifically in terms of neurite density and orientation dispersion or tract complexity.

Smaller changes in neurite density, measured by the NODDI parameter ICVF was observed with increasing age among younger to older adults. This was evident in both cross-sectional and longitudinal observations. This demonstrates that ICVF can detect longitudinal white matter changes in the absence of FA and MD changes. A plausible explanation could be that neurite density does not have a large contribution to FA (Zhang et al., 2012) and that changes in FA could be influenced by other contributing factors, primarily by axonal membranes (Beaulieu, 2002). Therefore, changes in neurite density can occur without significant impact on FA values. This further demonstrates the importance of measuring specific white matter changes as well as the utility of the NODDI parameter ICVF in detecting specific changes.

Tract orientation dispersion, measured by the NODDI parameter ODI, did not change significantly in longitudinal and cross-sectional analyses among older adults as well as in young to older adults. This is in contrast to a previous cross-sectional study which showed that orientation dispersion increases with age, suggesting that ODI is more sensitive to ageing than ICVF (Kodiweera et al., 2016). However, this was observed in a very small sample ($N = 47$) of young to middle-aged adults (i.e., 18 to 55 years old). Nonetheless, the sensitivity of ODI to ageing was also found in a bigger ($N = 702$), mixed cross-sectional and longitudinal study by Beck and colleagues (2021) on white matter microstructural changes in 18- to 94-year-olds. In a cross-sectional study on 3,513 UK Biobank participants (44 to 77 years old), ODI decreased as age increased (Cox et al., 2016). This demonstrates that differences and changes in ODI may not be similar between young and middle-aged adults and among older adults. While the above-mentioned UK Biobank study (Cox et al., 2016) may have a bigger sample with a younger age range that overlaps with the current study participants' age range, it was cross-sectionally-designed, whereas this study has shown both cross-sectionally and longitudinally that ODI differences and changes over time are not significant in older adults as well as among younger to older adults. The age effect on tract orientation dispersion is possibly very small and can be detected only in a very large sample.

Given that among young to older adults, cross-sectional differences in FA and MD were observed together with cross-sectional differences in ICVF but not in ODI, it is possible that changes in neurite density rather than changes in orientation dispersion or tract complexity contribute to changes in DTI parameters. Previously, it was found on a cross-sectional analysis that the association between older age and lower FA is driven by lower ICVF (Cox et al., 2016). On the other hand, when investigated among older adults alone, the current study results show no significant changes in ICVF both cross-sectionally and longitudinally. This suggests that annual changes in neurite density in older adults are smaller than expected and possibly driven by factors other than age itself.

4.2 Changes in executive functions in older age

The second study analysed longitudinal changes in executive functions and its associations with white matter changes, as measured by DTI and NODDI parameters in older adults aged 55 years and above. Changes in the DTI parameter MD were negatively associated with changes in executive functions indicating that the higher the annual changes in MD, the lower the annual changes in executive functions and vice-versa. This relationship was significant in the left internal capsule, parts of the sagittal stratum, parts of the posterior thalamic radiation, and white matter tracts in the temporal gyrus area.

While a few other tracts were involved, the association between white matter changes and executive functions were mainly found on the left internal capsule. This reflects the important role that the internal capsule plays in the performance of executive functions. The internal capsule contains both afferent and efferent white matter fibres that goes to and from the cerebral cortex and the thalamus and it is involved in several cognitive functions including executive functions (Mithani et al., 2020). Since executive functions involve goal-directed behavior involving thought (e.g., reasoning, planning) and movement or action inhibition (Koziol et al., 2012), it is expected that communication to and from the cerebral cortex occur and this information is conveyed through the internal capsule. In particular, the internal capsule carries information from the primary and supplementary motor areas, frontopontine and thalamic peduncles to the brain stem and cerebellar regions, and from thalamus to prefrontal cortex. The anatomical relevance of the internal capsule has been considered, especially in disorders implicating impairment of executive functions (e.g., Huys et al., 2019; Mithani et al, 2020; Zheng et al., 2014).

It is interesting to note that a significant left-lateralized effect was found. This was an unexpected finding given several studies showing reduced lateralization in ageing (Cabeza, 2002). Notwithstanding, this is consistent with functional studies showing a left-lateralized effect on executive function performance in early and pre-dementia stage (Schroeter et al., 2012). This left-lateralized effect was also found in a meta-analysis of functional studies on executive functions in healthy ageing using the Activation Likelihood Estimation (Heckner et al., 2020). It was suggested that this potentially reflects impairment in attention switching in older age. This functional left-lateralisation effect seems to be reflected structurally in the current study.

While there was a significant relationship between executive functions and changes in MD, there was no significant relationship between changes in FA and changes in executive functions. Previously, healthy older adults who showed higher FA also showed higher executive function performance (e.g., Grieve et al., 2007; Kennedy and Raz, 2009; Mayo et al., 2019). No such effects were found in the current study and there is evidence that FA and MD do not change simultaneously (Kawaguchi et al., 2010). One possible explanation is the cross-sectional nature of previous studies whereas the current study focused on longitudinal changes. Differences in tests that measure executive function performance could show different results therefore demonstrating the complexity of the relationship between white matter changes and cognitive performance. Furthermore, there is evidence that in comparison to FA and NODDI parameters, MD is more sensitive to microstructural decline in healthy ageing (Cox, et al., 2016). This is also evident in the diseased state (e.g., Gallagher et al., 2013; Yu et al., 2019;

Zheng et al., 2014) where the observed effects are larger. Longitudinally, there is evidence that FA in the internal capsule does not significantly change in 2 years in healthy adults aged between 50 and 90 years (Barrick et al., 2010). Furthermore, the fibres of the internal capsule also contain different orientation directions (Kawaguchi et al., 2010). This can impact on the estimation of FA (Oouchi et al., 2007; Winston, 2012), resulting in the underestimation of FA changes. Lastly, it is possible that an increase in FA due to fibre degeneration is counteracted by increasing MD (Chad et al., 2021). These previously described effects potentially explain the results in the current study where changes in FA had no significant relationship with changes in executive functions.

There was no significant relationship between neurite density and executive function performance. Similarly, there was no significant relationship between tract orientation dispersion and executive functions. These indicate that the NODDI parameters ICVF and ODI are potentially unable to capture effects of neurite density and orientation dispersion changes on executive functions. This could be due to the inability of the model to account for different fibre populations within the voxel (i.e., crossing or kissing fibres) and therefore tract-specific changes could not be distinguished (Dhollander et al., 2021). Furthermore, since neurite density and orientation dispersion are measured within voxel, it does not capture macrostructural white matter changes such as white matter lesion volume that impact on executive function performance (Bolandzadeh et al., 2012; Verdelho et al., 2007; Vernooij et al., 2009). Previously, it has been shown that both microstructural and macrostructural white matter characteristics contribute to cognitive performance (Fjell et al., 2012, 2017b). It has been proposed that a combined measure of fibre density and fibre bundle cross-section is more likely to capture white matter changes associated with cognitive changes because it accounts for both microstructural and macrostructural white matter properties (Raffelt et al., 2017).

The relationship between brain state and changes in executive function performance was also analyzed. Lower white matter integrity observed in association, projection, and callosal fibre tracts is associated with greater changes in executive functions over time. Consistent with the current study result on the relationship between white matter changes and changes in executive functions, this relationship between brain state and cognitive changes was captured by MD but not by FA, ICVF, or ODI. The state of several white matter tracts significantly impacted on changes in executive functions and this suggests the importance of inter- and intra-hemispheric communication and coordination in the performance of executive functions. This reflects the multiple aspects of executive functions such as cognitive processing, integration of information, and action or inhibition of action. Older adults with lower MD, indicating greater white matter integrity, showed less change in executive functions over time.

Those with higher MD, indicating lower white matter integrity, showed greater changes in executive functions. This likely reflects lifestyle such as engagement in novel cognitive activity and physiological factors such as levels of pulse pressure, speed of gait, body mass index (BMI) levels, and balance (Caballero et al., 2021) which influence the change or stability of executive function performance over time.

4.3 Strengths and limitations of the studies and future directions

In the first study, there was a relatively large sample size with a wide age range and with older adults well-represented. Two separate analyses were also conducted on young to older adults and on older adults alone which showed age effects evident when young adults are included in the analysis and age effects evident in older adults alone. Furthermore, both cross-sectional and longitudinal data were available which allowed for comparison of cross-sectional and longitudinal analyses on DTI and NODDI parameters. Based on current knowledge, there is only one other study that investigated both cross-sectional differences and longitudinal white matter changes in non-pathological ageing. This study by Barrick and colleagues (2010) involved participants with a similar age range (50 to 90 years) to the older adults in the current study. However, it did not include analysis on young to older adults and the sample size was small (N = 73). It also employed only DTI parameters. A study by Cox and colleagues (2016) had a big sample (N = 3513) and included both DTI and NODDI parameters. However, this was only cross-sectional analysis. Given the dearth of studies on white matter cross-sectional differences and longitudinal changes in normal ageing using both DTI and NODDI parameters, the current study provides valuable contribution to literature.

The relationship between executive functions and the brain has been previously explored mainly through cross-sectional functional studies. Thus, the strength of the second study is the longitudinal approach to investigating the association between white matter tracts and changes in executive functions over time in a relatively large sample of population-based healthy older adults. Furthermore, the limited number of studies used standard diffusion MRI parameters which are non-specific. This study implemented the NODDI model which is an advanced biophysical model that allowed for more specific observations of changes in neurite density and orientation dispersion.

Both studies had the advantage of implementing an advanced registration pipeline, DTI-TK, which uses full tensor information. This tensor-based pipeline has a higher specificity and precision (Keihaninejad et al., 2013) and is the recommended registration technique for use with TBSS along with study-specific registration target and skeletonisation (Bach et al., 2014). The TBSS approach is highly reproducible and lends to future meta-analyses as it is a highly

standardized approach (Beck et al., 2021). It is also worth noting that participants were scanned on the same scanner thus eliminating potential confounds due to scanner differences.

The limitations of the studies include the inability of the NODDI and DTI model to distinguish crossing and kissing fibres, notwithstanding the generation of white matter skeletons from FA. Thus, future studies could include models that can differentiate mixed fibres within a voxel or use a non-voxel-based analysis such as a fixel-based analysis (e.g., Arun et al., 2021; Dhollander et al., 2021). It would be also interesting to see if results from other models, particularly those that are able to resolve crossing fibres such as constrained spherical deconvolution, would support the findings in this study.

Furthermore, two cross-sectional data were also analysed in this sample of 1000Brains study participants (i.e., data from the first time point and data from the second time point), in an attempt to replicate the results. However, it is acknowledged that an independent comparable sample would be desirable for future studies to replicate and cross-validate the results of this study.

It was found that at age 55 and onwards, there are no significant differences or changes in both DTI and NODDI parameters. Future work could investigate exactly when age effects are no longer detected and identify non-age-related sources of white matter variability.

Longitudinal changes in executive functions and its associations with white matter changes were also measured by DTI and NODDI parameters in older adults aged 55 years and above. A major limitation of the second study was that inter-individual differences between subjects and intra-individual changes in executive functions were not investigated. Based on the raw data, longitudinal changes in executive functions observed were heterogeneous and this could be indicative of inter-individual variability. For some individuals, there was an increase in executive functions over time while for some there was a decrease. This heterogeneity of change as well as whether the changes in executive functions within the individual are significant or not would be interesting to explore in further studies. Previously, a longitudinal study found significant individual variability in changes and levels of executive function performance among a large group of community-dwelling older adults (Caballero et al., 2021). Other studies such as by Goh and colleagues (2012) have also reported heterogeneous longitudinal changes either as a decline, relative stability, or improvement in executive function performance. It is possible that practice effects may have played a role, resulting in an improvement of executive function performance in some individuals. However, there has been evidence that while it may contribute to longitudinal changes, practice effects cannot fully account for an increase in cognitive performance (Salthouse, 2010). Heterogeneity of change has been predicted by multiple factors such as levels of education, engagement in novel

cognitive activity, levels of pulse pressure, age, speed of gait, body mass index levels, and balance (Caballero et al., 2021). In the current study, levels of education and age were controlled for but lifestyle and other factors were not. These uncontrolled factors possibly contributed to the observed heterogeneous changes in executive functions.

Given that the association between white matter changes and executive functions was a left-lateralized effect on the internal capsule, it would be interesting for future studies to test if the left internal capsule declines faster than the right internal capsule. This might explain the asymmetry in changes observed in the second study.

In summary, the first study showed that in a sample with a broad age range, inter-individual changes in FA, MD, ICVF, and ODI do not necessarily reflect intra-individual changes in these parameters. It has demonstrated this by studying cross-sectional and longitudinal white matter changes using DTI and NODDI parameters on the same individuals. It was found that the NODDI parameter ICVF, which is a putative measure for neurite density, can detect longitudinal changes even in the absence of changes in DTI parameters FA and MD. It was also demonstrated that there are no age-related differences in white matter microstructure, as measured by DTI and NODDI parameters, among older adults from age 55 years onwards. This was consistently observed cross-sectionally and longitudinally. In this current sample of neurologically healthy older adults, annual change in neurite density and orientation dispersion are possibly not due to ageing per se, indicating that age is not a major contributor to brain microstructural decline in older age. Therefore, when examining these white matter changes, it is important to consider other potential factors such as lifestyle and cognitive abilities, rather than focus on age.

Both the DTI model and the NODDI model were used to explore the relationship between executive functions and white matter microstructure. Longitudinal changes in executive functions were associated with longitudinal changes primarily in the left internal capsule. On the other hand, the integrity of the association, projection, and callosal fibres were associated with changes in executive functions over time. These relationships were captured by MD, indicating that the MD parameter is more sensitive to microstructural changes compared to FA and to NODDI parameters ICVF and ODI. This suggests that microstructural changes associated with executive functions are potentially driven by factors other than neurite density and tract orientation dispersion.

The relationship between changes in the internal capsule and changes in executive functions reflect the anatomical relevance of the internal capsule in cognitive processing and behavior (i.e., action or inhibition). Furthermore, the relationships between the integrity of the association, projection, and callosal fibres and changes in executive functions suggests that

importance of communication and coordination among several tracts in the cognitive processing, integration of information, and the resulting action or inhibition of action that make up successful executive function performance.

Heterogeneity of white matter microstructural changes is an important consideration in investigating individual differences and potentially play a role in changes in executive functions in ageing. These individual differences are driven by various risks and protective factors such as those outlined by Caballero and colleagues (2021), creating the possibility for potential interventions aimed at preventing the decline of executive functions in older age.

5 Reference list

Alexander, A.L., Lee, J.E., Lazar, M. and Field, A.S., 2007. Diffusion tensor imaging of the brain. Neurotherapeutics, 4(3), pp.316-329. https://doi.org/10.1016/j.nurt.2007.05.011

Alexander, A.L., Hurley, S.A., Samsonov, A.A., Adluru, N., Hosseinbor, A.P., Mossahebi, P., Tromp, D.P., Zakszewski, E. and Field, A.S., 2011. Characterization of cerebral white matter properties using quantitative magnetic resonance imaging stains. Brain connectivity, 1(6), pp.423-446. https://doi.org/10.1089/brain.2011.0071

Anderton, B.H., 2002. Ageing of the brain. Mechanisms of ageing and development, 123(7), pp.811-817. https://doi.org/10.1016/S0047-6374(01)00426-2

Arun, A.H., Connelly, A., Smith, R.E. and Calamante, F., 2021. Characterisation of white matter asymmetries in the healthy human brain using diffusion MRI fixel-based analysis. Neuroimage, 225, p.117505. https://doi.org/10.1016/j.neuroimage.2020.117505

Bach, M., Laun, F.B., Leemans, A., Tax, C.M., Biessels, G.J., Stieltjes, B. and Maier-Hein, K.H., 2014. Methodological considerations on tract-based spatial statistics (TBSS). Neuroimage, 100, pp.358-369. https://doi.org/10.1016/j.neuroimage.2014.06.021

Barrick, T.R., Charlton, R.A., Clark, C.A. and Markus, H.S., 2010. White matter structural decline in normal ageing: a prospective longitudinal study using tract-based spatial statistics. Neuroimage, 51(2), pp.565-577. https://doi.org/10.1016/j.neuroimage.2010.02.033

Basser, P. J., & Pierpaoli, C.,1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. Journal of magnetic resonance series B, 111(3), pp. 209–219. https://doi.org/10.1016/j.jmr.2011.09.022

Bastiani, M., Cottaar, M., Fitzgibbon, S.P., Suri, S., Alfaro-Almagro, F., Sotiropoulos, S.N., Jbabdi, S. and Andersson, J.L., 2019. Automated quality control for within and between studies diffusion MRI data using a non-parametric framework for movement and distortion correction. Neuroimage, 184, pp.801-812. https://doi.org/10.1016/j.neuroimage.2018.09.073

Bäumler, G., & Stroop, J. (1985). Farbe-Wort-Interferenztest nach JR Stroop (FWIT).

Hogrefe, Verlag für Psychologie.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system – a technical review. NMR in biomedicine: an international journal devoted to the development and application of magnetic resonance in vivo, 15(7-8), pp.435-455. https://doi.org/10.1002/nbm.782

Beck, D., de Lange, A.M.G., Maximov, I.I., Richard, G., Andreassen, O.A., Nordvik, J.E. and Westlye, L.T., 2021. White matter microstructure across the adult lifespan: A mixed longitudinal and cross-sectional study using advanced diffusion models and brain-age prediction. Neuroimage, 224, p.117441. https://doi.org/10.1016/j.neuroimage.2020.117441

Bendlin, B.B., Fitzgerald, M.E., Ries, M.L., Xu, G., Kastman, E.K., Thiel, B.W., Rowley, H.A., Lazar, M., Alexander, A.L. and Johnson, S.C., 2010. White matter in aging and cognition: a cross-sectional study of microstructure in adults aged eighteen to eighty-three. Developmental neuropsychology, 35(3), pp.257-277. https://doi.org/10.1080/87565641003696775

Benjamini, Y. and Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the royal statistical society: series B (Methodological), 57(1), pp.289-300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bennett, I.J. and Madden, D.J., 2014. Disconnected aging: cerebral white matter integrity and age-related differences in cognition. Neuroscience, 276, pp.187-205. https://doi.org/10.1016/j.neuroscience.2013.11.026

Bennett, I.J., Madden, D.J., Vaidya, C.J., Howard, D.V. and Howard Jr, J.H., 2010. Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. Human brain mapping, 31(3), pp.378-390. https://doi.org/10.1002/hbm.20872

Blain, C.R., Williams, V.C., Johnston, C., Stanton, B.R., Ganesalingam, J., Jarosz, J.M., Jones, D.K., Barker, G.J., Williams, S.C., Leigh, N.P. and Simmons, A., 2007. A longitudinal study of diffusion tensor MRI in ALS. Amyotrophic lateral sclerosis, 8(6), pp.348-355. https://doi.org/10.1080/17482960701548139

Bolandzadeh, N., Davis, J.C., Tam, R., Handy, T.C. and Liu-Ambrose, T., 2012. The association between cognitive function and white matter lesion location in older adults: a systematic review. BMC neurology, 12(1), pp.1-10. https://doi.org/10.1186/1471-2377-12-126

Borghesani, P.R., Madhyastha, T.M., Aylward, E.H., Reiter, M.A., Swarny, B.R., Schaie, K.W. and Willis, S.L., 2013. The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging. Neuropsychologia, 51(8), pp.1435-1444. https://doi.org/10.1016/j.neuropsychologia.2013.03.005

Burzynska, A.Z., Preuschhof, C., Bäckman, L., Nyberg, L., Li, S.C., Lindenberger, U. and Heekeren, H.R., 2010. Age-related differences in white matter microstructure: region-specific patterns of diffusivity. Neuroimage, 49(3), pp.2104-2112. https://doi.org/10.1016/j.neuroimage.2009.09.041

Caballero, H.S., McFall, G.P., Wiebe, S.A. and Dixon, R.A., 2021. Integrating three characteristics of executive function in non-demented aging: trajectories, classification, and biomarker predictors. Journal of the international neuropsychological society, 27(2), pp.158-171. https://doi.org/10.1017/S1355617720000703

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychology and aging, 17(1), p.85. https://doi.org/10.1037/0882-7974.17.1.85

Cahn-Weiner, D.A., Boyle, P.A. and Malloy, P.F., 2002. Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. Applied neuropsychology, 9(3), pp.187-191. https://doi.org/10.1207/S15324826AN0903_8

Caspers, S., Moebus, S., Lux, S., Pundt, N., Schütz, H., Mühleisen, T.W., Gras, V., Eickhoff, S.B., Romanzetti, S., Stöcker, T. and Stirnberg, R., 2014. Studying variability in human brain aging in a population-based German cohort—rationale and design of 1000BRAINS. Frontiers in aging neuroscience, 6, p.149. https://doi.org/10.3389/fnagi.2014.00149

Chad, J.A., Pasternak, O. and Chen, J.J., 2021. Orthogonal moment diffusion tensor decomposition reveals age-related degeneration patterns in complex fiber architecture. Neurobiology of aging, 101, pp.150-159. https://doi.org/10.1016/j.neurobiolaging.2020.12.020

Chang, Y.S., Owen, J.P., Pojman, N.J., Thieu, T., Bukshpun, P., Wakahiro, M.L., Berman, J.I., Roberts, T.P., Nagarajan, S.S., Sherr, E.H. and Mukherjee, P., 2015. White matter changes of neurite density and fiber orientation dispersion during human brain maturation. PloS one, 10(6), p.e0123656. https://doi.org/10.1371/journal.pone.0123656

Charlton, R.A., Barrick, T.R., McIntyre, D.J., Shen, Y., O'Sullivan, M., Howe, F.A., Clark, C.A., Morris, R.G. and Markus, H.S., 2006. White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. Neurology, 66(2), pp.217-222. https://doi.org/10.1212/01.wnl.0000194256.15247.83

Charlton, R.A., Schiavone, F., Barrick, T.R., Morris, R.G. and Markus, H.S., 2010. Diffusion tensor imaging detects age related white matter change over a 2-year follow-up which is associated with working memory decline. Journal of neurology, neurosurgery & psychiatry, 81(1), pp.13-19. https://doi.org/10.1136/jnnp.2008.167288

Christensen, H., 2001. What cognitive changes can be expected with normal ageing? Australian & New Zealand journal of psychiatry, 35(6), pp.768-775. https://doi.org/10.1046/j.1440-1614.2001.00966.x

Coelho, A., Fernandes, H.M., Magalhães, R., Moreira, P.S., Marques, P., Soares, J.M., Amorim, L., Portugal-Nunes, C., Castanho, T., Santos, N.C. and Sousa, N., 2021. Signatures of white-matter microstructure degradation during aging and its association with cognitive status. Scientific reports, 11(1), pp.1-12. https://doi.org/10.1038/s41598-021-83983-7

Cox, S.R., Ritchie, S.J., Tucker-Drob, E.M., Liewald, D.C., Hagenaars, S.P., Davies, G., Wardlaw, J.M., Gale, C.R., Bastin, M.E. and Deary, I.J., 2016. Ageing and brain white matter structure in 3,513 UK Biobank participants. Nature communications, 7(1), p.13629. https://doi.org/10.1038/ncomms13629

Davis, S.W., Dennis, N.A., Buchler, N.G., White, L.E., Madden, D.J. and Cabeza, R., 2009. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. Neuroimage, 46(2), pp.530-541. https://doi.org/10.1016/j.neuroimage.2009.01.068

de Groot, M., Cremers, L.G., Ikram, M.A., Hofman, A., Krestin, G.P., van der Lugt, A., Niessen, W.J. and Vernooij, M.W., 2016. White matter degeneration with aging: longitudinal diffusion MR imaging analysis. Radiology, 279(2), pp.532-541. https://doi.org/10.1148/radiol.2015150103

Dhollander, T., Clemente, A., Singh, M., Boonstra, F., Civier, O., Duque, J.D., Egorova, N., Enticott, P., Fuelscher, I., Gajamange, S. and Genc, S., 2021. Fixel-based analysis of diffusion MRI: methods, applications, challenges and opportunities. Neuroimage, 241, p.118417. https://doi.org/10.1016/j.neuroimage.2021.118417

Dickstein, D.L., Weaver, C.M., Luebke, J.I. and Hof, P.R., 2013. Dendritic spine changes associated with normal aging. Neuroscience, 251, pp.21-32. https://doi.org/10.1016/j.neuroscience.2012.09.077

Esiri, M.M., 2007. Ageing and the brain. The journal of pathology: a journal of the pathological society of Great Britain and Ireland, 211(2), pp.181-187. https://doi.org/10.1002/path.2089

Farokhian, F., Yang, C., Beheshti, I., Matsuda, H. and Wu, S., 2017. Age-related gray and white matter changes in normal adult brains. Aging and disease, 8(6), pp.899-909. https://doi.org/10.14336/AD.2017.0502

Fjell, A.M. and Walhovd, K.B., 2010. Structural brain changes in aging: courses, causes and cognitive consequences. Reviews in the neurosciences, 21(3), pp.187-222. https://doi.org/10.1515/REVNEURO.2010.21.3.187

Fjell, A.M., Sneve, M.H., Grydeland, H., Storsve, A.B., Amlien, I.K., Yendiki, A. and Walhovd, K.B., 2017a. Relationship between structural and functional connectivity change across the adult lifespan: a longitudinal investigation. Human brain mapping, 38(1), pp.561-573. https://doi.org/10.1002/hbm.23403

Fjell, A.M., Sneve, M.H., Grydeland, H., Storsve, A.B. and Walhovd, K.B., 2017b. The disconnected brain and executive function decline in aging. Cerebral cortex, 27(3), pp.2303-2317. https://doi.org/10.1093/cercor/bhw082

Fjell, A.M., Westlye, L.T., Amlien, I.K. and Walhovd, K.B., 2012. A multi-modal investigation of behavioral adjustment: post-error slowing is associated with white matter characteristics. Neuroimage, 61(1), pp.195-205. https://doi.org/10.1016/j.neuroimage.2012.03.007

Gallagher, C., Bell, B., Bendlin, B., Palotti, M., Okonkwo, O., Sodhi, A., Wong, R., Buyan-Dent, L., Johnson, S., Willette, A. and Harding, S., 2013. White matter microstructural integrity and executive function in Parkinson's disease. Journal of the international neuropsychological society, 19(3), p.349 -354. https://doi.org/10.1017/S1355617712001373

Gaser, C., Dahnke, R., Thompson, P.M., Kurth, F., Luders, E. and Alzheimer's Disease Neuroimaging Initiative, 2024. CAT: a computational anatomy toolbox for the analysis of structural MRI data. Gigascience, 13, p.giae049. https://doi.org/10.1093/gigascience/giae049

Ge, Y., Grossman, R.I., Babb, J.S., Rabin, M.L., Mannon, L.J. and Kolson, D.L., 2002. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. American journal of neuroradiology, 23(8), pp.1327-1333.

Goh, J.O., An, Y. and Resnick, S.M., 2012. Differential trajectories of age-related changes in components of executive and memory processes. Psychology and aging, 27(3), p.707. https://doi.org/10.1037/a0026715

Gozdas, E., Fingerhut, H., Dacorro, L., Bruno, J.L. and Hosseini, S.H., 2021. Neurite imaging reveals widespread alterations in gray and white matter neurite morphology in healthy aging and amnestic mild cognitive impairment. Cerebral cortex, 31(12), pp.5570-5578. https://doi.org/10.1093/cercor/bhab180

Grieve, S.M., Williams, L.M., Paul, R.H., Clark, C.R. and Gordon, E., 2007. Cognitive aging, executive function, and fractional anisotropy: a diffusion tensor MR imaging study. American journal of neuroradiology, 28(2), pp.226-235

Grussu, F., Schneider, T., Tur, C., Yates, R.L., Tachrount, M., Ianuş, A., Yiannakas, M.C., Newcombe, J., Zhang, H., Alexander, D.C., DeLuca, G.C., Gandini Wheeler-Kingshott, C.A.M., 2017. Neurite dispersion: a new marker of multiple sclerosis spinal cord pathology? Annals of clinical and translational neurology, 4, pp. 663–679. https://doi.org/10.1002/acn3.445

Guttmann, C.R., Jolesz, F.A., Kikinis, R., Killiany, R.J., Moss, M.B., Sandor, T. and Albert, M.S., 1998. White matter changes with normal aging. Neurology, 50(4), pp.972-978. https://doi.org/10.1212/WNL.50.4.972

Hayes, S.M., Salat, D.H., Forman, D.E., Sperling, R.A. and Verfaellie, M., 2015. Cardiorespiratory fitness is associated with white matter integrity in aging. Annals of clinical and translational neurology, 2(6), pp.688-698. https://doi.org/10.1002/acn3.204

Heckner, M.K., Cieslik, E.C., Eickhoff, S.B., Camilleri, J.A., Hoffstaedter, F. and Langner, R., 2020. The Aging Brain and Executive Functions Revisited: Implications from Meta-Analytic and Functional-Connectivity Evidence. Journal of cognitive neuroscience, pp.1-37. https://doi.org/10.1162/jocn_a_01616

Heiervang, E., Behrens, T.E.J., Mackay, C.E., Robson, M.D. and Johansen-Berg, H., 2006. Between session reproducibility and between subject variability of diffusion MR and tractography measures. Neuroimage, 33(3), pp.867-877. https://doi.org/10.1016/j.neuroimage.2006.07.037

Higby, E., Cahana-Amitay, D., Vogel-Eyny, A., Spiro III, A., Albert, M.L. and Obler, L.K., 2019. The role of executive functions in object-and action-naming among older adults. Experimental aging research, 45(4), pp.306-330. https://doi.org/10.1080/0361073X.2019.1627492

Huys, D., Kohl, S., Baldermann, J.C., Timmermann, L., Sturm, V., Visser-Vandewalle, V. and Kuhn, J., 2019. Open-label trial of anterior limb of internal capsule–nucleus accumbens deep brain stimulation for obsessive-compulsive disorder: insights gained. Journal of neurology, neurosurgery & psychiatry, 90(7), pp.805-812. https://doi.org/10.1136/jnnp-2018-318996

Jernigan, T.L., Archibald, S.L., Fennema-Notestine, C., Gamst, A.C., Stout, J.C., Bonner, J. and Hesselink, J.R., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiology of aging, 22(4), pp.581-594. https://doi.org/10.1016/S0197-4580(01)00217-2

Jones, D.K., 2008. Studying connections in the living human brain with diffusion MRI. Cortex, 44(8), pp.936-952. https://doi.org/10.1016/j.cortex.2008.05.002

Kalbe, E., Kessler, J., Calabrese, P., Smith, R., Passmore, A.P., Brand, M.A. and Bullock, R., 2004. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. International journal of geriatric psychiatry, 19(2), pp.136-143. https://doi.org/10.1002/gps.1042

Kaiser, H.F., 1974. An index of factorial simplicity. Psychometrika, 39(1), pp.31-36. https://doi.org/10.1007/BF02291575

Kamiya, K., Hori, M. and Aoki, S., 2020. NODDI in clinical research. Journal of neuroscience methods, 346, p.108908. https://doi.org/10.1016/j.jneumeth.2020.108908

Kantarci, K., Senjem, M.L., Avula, R., Zhang, B., Samikoglu, A.R., Weigand, S.D., Przybelski, S.A., Edmonson, H.A., Vemuri, P., Knopman, D.S. and Boeve, B.F., 2011. Diffusion tensor imaging and cognitive function in older adults with no dementia. Neurology, 77(1), pp.26-34. https://doi.org/10.1212/WNL.0b013e31822313dc

Keihaninejad, S., Zhang, H., Ryan, N.S., Malone, I.B., Modat, M., Cardoso, M.J., Cash, D.M., Fox, N.C. and Ourselin, S., 2013. An unbiased longitudinal analysis framework for tracking white matter changes using diffusion tensor imaging with application to Alzheimer's disease. Neuroimage, 72, pp.153-163. https://doi.org/10.1016/j.neuroimage.2013.01.044

Kennedy, K.M. and Raz, N., 2009. Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia, 47(3), pp.916-927. https://doi.org/10.1016/j.neuropsychologia.2009.01.001

Knopman, D.S., Jack Jr, C.R., Wiste, H.J., Weigand, S.D., Vemuri, P., Lowe, V.J., Kantarci, K., Gunter, J.L., Senjem, M.L., Mielke, M.M. and Roberts, R.O., 2013. Brain injury biomarkers are not dependent on β-amyloid in normal elderly. Annals of neurology, 73(4), pp.472-480. https://doi.org/10.1002/ana.23816

Kodiweera, C., Alexander, A.L., Harezlak, J., McAllister, T.W. and Wu, Y.C., 2016. Age effects and sex differences in human brain white matter of young to middle-aged adults: A DTI, NODDI, and q-space study. Neuroimage, 128, pp.180-192. https://doi.org/10.1016/j.neuroimage.2015.12.033

Koziol, L.F., Budding, D.E. and Chidekel, D., 2012. From movement to thought: executive function, embodied cognition, and the cerebellum. The cerebellum, 11(2), pp.505-525. https://doi.org/10.1007/s12311-011-0321-y

Kuchling, J., Backner, Y., Oertel, F.C., Raz, N., Bellmann-Strobl, J., Ruprecht, K., Paul, F., Levin, N., Brandt, A.U. and Scheel, M., 2018. Comparison of probabilistic tractography and tract-based spatial statistics for assessing optic radiation damage in patients with autoimmune inflammatory disorders of the central nervous system. Neuroimage: clinical, 19, pp.538-550. https://doi.org/10.1016/j.nicl.2018.05.004

Lawrence, K.E., Nabulsi, L., Santhalingam, V., Abaryan, Z., Villalon-Reina, J.E., Nir, T.M., Ba Gari, I., Zhu, A.H., Haddad, E., Muir, A.M. and Laltoo, E., 2021. Age and sex effects on advanced white matter microstructure measures in 15,628 older adults: A UK biobank study. Brain imaging and behavior, 15(6), pp.2813-2823. https://doi.org/10.1007/s11682-021-00548-y

Lebel, C. and Beaulieu, C., 2011. Longitudinal development of human brain wiring continues from childhood into adulthood. Journal of neuroscience, 31(30), pp.10937-10947. https://doi.org/10.1523/JNEUROSCI.5302-10.2011

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W. and Beaulieu, C., 2012. Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage, 60(1), pp.340-352. https://doi.org/10.1016/j.neuroimage.2011.11.094

Lin, M., He, H., Schifitto, G. and Zhong, J., 2016. Simulation of changes in diffusion related to different pathologies at cellular level after traumatic brain injury. Magnetic resonance in medicine, 76(1), pp.290-300. https://doi.org/10.1002/mrm.25816

Marner, L., Nyengaard, J.R., Tang, Y. and Pakkenberg, B., 2003. Marked loss of myelinated nerve fibers in the human brain with age. Journal of comparative neurology, 462(2), pp.144-152. https://doi.org/10.1002/cne.10714

Mayo, C.D., Garcia-Barrera, M.A., Mazerolle, E.L., Ritchie, L.J., Fisk, J.D., Gawryluk, J.R. and Alzheimer's Disease Neuroimaging Initiative, 2019. Relationship between DTI metrics and cognitive function in Alzheimer's disease. Frontiers in aging neuroscience, 10, p.436. https://doi.org/10.3389/fnagi.2018.00436

Merluzzi, A.P., Dean III, D.C., Adluru, N., Suryawanshi, G.S., Okonkwo, O.C., Oh, J.M., Hermann, B.P., Sager, M.A., Asthana, S., Zhang, H. and Johnson, S.C., 2016. Age-dependent differences in brain tissue microstructure assessed with neurite orientation dispersion and density imaging. Neurobiology of aging, 43, pp.79-88. https://doi.org/10.1016/j.neurobiolaging.2016.03.026

Mithani, K., Davison, B., Meng, Y. and Lipsman, N., 2020. The anterior limb of the internal capsule: Anatomy, function, and dysfunction. Behavioural brain research, 387, p.112588. https://doi.org/10.1016/j.bbr.2020.112588

Modat, M., Ridgway, G.R., Taylor, Z.A., Lehmann, M., Barnes, J., Hawkes, D.J., Fox, N.C. and Ourselin, S., 2010. Fast free-form deformation using graphics processing units. Computer methods and programs in biomedicine, 98(3), pp.278-284. https://doi.org/10.1016/j.cmpb.2009.09.002

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A.V., Mahmood, A., Woods, R. and Toga, A.W., 2008. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage, 40(2), pp.570-582. https://doi.org/10.1016/j.neuroimage.2007.12.035

Morris, J.C., Heyman, A., Mohs, R.C., Hughes, J.P., van Belle, G., Fillenbaum, G.D.M.E., Mellits, E.D. and Clark, C., 1989. The Consortium to Establish a Registry for Alzheimer's

Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology, 39(9), pp.1159-1165. https://doi.org/10.1212/wnl.39.9.1159

Motovylyak, A., Vogt, N.M., Adluru, N., Ma, Y., Wang, R., Oh, J.M., Kecskemeti, S.R., Alexander, A.L., Dean, D.C., Gallagher, C.L. and Sager, M.A., 2022. Age-related differences in white matter microstructure measured by advanced diffusion MRI in healthy older adults at risk for Alzheimer's disease. Aging brain, 2, p.100030. https://doi.org/10.1016/j.nbas.2022.100030

Nuninga, J.O., Mandl, R.C., Froeling, M., Siero, J.C., Somers, M., Boks, M.P., Nieuwdorp, W., Heringa, S. and Sommer, I.E., 2020. Vasogenic edema versus neuroplasticity as neural correlates of hippocampal volume increase following electroconvulsive therapy. Brain stimulation, 13(4), pp.1080-1086. https://doi.org/10.1016/j.brs.2020.04.017

Ogawa, C., Kidokoro, H., Fukasawa, T., Yamamoto, H., Ishihara, N., Ito, Y., Sakaguchi, Y., Okai, Y., Ohno, A., Nakata, T. and Azuma, Y., 2018. Cytotoxic edema at onset in West syndrome of unknown etiology: A longitudinal diffusion tensor imaging study. Epilepsia, 59(2), pp.440-448. https://doi.org/10.1111/epi.13988

Oishi, K., Faria, A.V., Van Zijl, P.C. and Mori, S., 2010. MRI atlas of human white matter. Academic Press.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9(1), pp.97-113. https://doi.org/10.1016/0028-3932(71)90067-4

Oouchi, H., Yamada, K., Sakai, K., Kizu, O., Kubota, T., Ito, H. and Nishimura, T., 2007. Diffusion anisotropy measurement of brain white matter is affected by voxel size: underestimation occurs in areas with crossing fibers. American journal of neuroradiology, 28(6), pp.1102-1106. https://doi.org/10.3174/ajnr.A0488

O'Sullivan, M.R.C.P., Jones, D.K., Summers, P.E., Morris, R.G., Williams, S.C.R. and Markus, H.S., 2001. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology, 57(4), pp.632-638. https://doi.org/10.1212/WNL.57.4.632

Pannese E., 2011. Morphological changes in nerve cells during normal aging. Brain structure and function, 216(2), pp.85-89. https://doi.org/10.1007/s00429-011-0308-y

Park, D.C., Polk, T.A., Mikels, J.A., Taylor, S.F. and Marshuetz, C., 2001. Cerebral aging: integration of brain and behavioral models of cognitive function. Dialogues in clinical neuroscience, 3(3), p.151. https://doi.org/10.31887/DCNS.2001.3.3/dcpark

Pierpaoli, C. and Basser, P.J., 1996. Toward a quantitative assessment of diffusion anisotropy. Magnetic resonance in medicine, 36(6), pp.893-906. https://doi.org/10.1002/mrm.1910360612

Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A. and Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. Radiology, 201(3), pp.637-648. https://doi.org/10.1148/radiology.201.3.8939209

Preziosa, P., Pagani, E., Meani, A., Marchesi, O., Conti, L., Falini, A., Rocca, M.A. and Filippi, M., 2023. NODDI, diffusion tensor microstructural abnormalities and atrophy of brain white matter and gray matter contribute to cognitive impairment in multiple sclerosis. Journal of Neurology, 270(2), pp.810-823. https://doi.org/10.1007/s00415-022-11415-1

Raffelt, D.A., Tournier, J.D., Smith, R.E., Vaughan, D.N., Jackson, G., Ridgway, G.R. and Connelly, A., 2017. Investigating white matter fibre density and morphology using fixel-based analysis. Neuroimage, 144, pp.58-73. https://doi.org/10.1016/j.neuroimage.2016.09.029

Raghavan, S., Reid, R.I., Przybelski, S.A., Lesnick, T.G., Graff-Radford, J., Schwarz, C.G., Knopman, D.S., Mielke, M.M., Machulda, M.M., Petersen, R.C. and Jack Jr, C.R., 2021. Diffusion models reveal white matter microstructural changes with ageing, pathology and cognition. Brain communications, 3(2), p.fcab106. https://doi.org/10.1093/braincomms/fcab106

Rai, V., Nath, K., Saraswat, V.A., Purwar, A., Rathore, R.K. and Gupta, R.K., 2008. Measurement of cytotoxic and interstitial components of cerebral edema in acute hepatic failure by diffusion tensor imaging. Journal of magnetic resonance imaging 28(2), pp.334-341. https://doi.org/10.1002/jmri.21438

Regard, M., Strauss, E., & Knapp, P., 1982. Children's production on verbal and nonverbal fluency tasks. Perceptual and motor skills, 55(3), 839-844. https://doi.org/10.2466/pms.1982.55.3.839

Resnick, S.M., Goldszal, A.F., Davatzikos, C., Golski, S., Kraut, M.A., Metter, E.J., Bryan, R.N., Zonderman, A.B., 2000. One-year age changes in MRI brain volumes in older adults. Cerebral cortex, 10(5), pp.464-472. https://doi.org/10.1093/cercor/10.5.464

Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S., Busa, E., Morris, J.C., Dale, A.M. and Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cerebral cortex, 14(7), pp.721-730. https://doi.org/10.1093/cercor/bhh032

Salat, D.H., Tuch, D.S., Greve, D.N., Van Der Kouwe, A.J.W., Hevelone, N.D., Zaleta, A.K., Rosen, B.R., Fischl, B., Corkin, S., Rosas, H.D. and Dale, A.M., 2005. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiology of aging, 26(8), pp.1215-1227. https://doi.org/10.1016/j.neurobiolaging.2004.09.017

Salthouse, T.A., 2010. Influence of age on practice effects in longitudinal neurocognitive change. Neuropsychology, 24(5), p.563. https://doi.org/10.1037/a0019026

Sasson, E., Doniger, G.M., Pasternak, O., Tarrasch, R. and Assaf, Y., 2013. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. Frontiers in neuroscience, 7, p.32. https://doi.org/10.3389/fnins.2013.00032

Scahill, R.I., Frost, C., Jenkins, R., Whitwell, J.L., Rossor, M.N. and Fox, N.C., 2003. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Archives of neurology, 60(7), pp.989-994. https://doi.org/10.1001/archneur.60.7.989

Schilling, K.G., Janve, V., Gao, Y., Stepniewska, I., Landman, B.A., Anderson, A.W., 2018. Histological validation of diffusion MRI fiber orientation distributions and dispersion. Neuroimage 165, 200–221. https://doi.org/10.1016/j.neuroimage.2017.10.046

Schilling, K.G., Tax, C.M., Rheault, F., Landman, B.A., Anderson, A.W., Descoteaux, M. and Petit, L., 2022. Prevalence of white matter pathways coming into a single white matter

voxel orientation: The bottleneck issue in tractography. Human brain mapping, 43(4), pp.1196-1213. https://doi.org/10.1002/hbm.25697

Schroeter, M.L., Vogt, B., Frisch, S., Becker, G., Barthel, H., Mueller, K., Villringer, A. and Sabri, O., 2012. Executive deficits are related to the inferior frontal junction in early dementia. Brain, 135(1), pp.201-215. https://doi.org/10.1093/brain/awr311

Sexton, C.E., Walhovd, K.B., Storsve, A.B., Tamnes, C.K., Westlye, L.T., Johansen-Berg, H. and Fjell, A.M., 2014. Accelerated changes in white matter microstructure during aging: a longitudinal diffusion tensor imaging study. Journal of neuroscience, 34(46), pp.15425-15436. https://doi.org/10.1523/JNEUROSCI.0203-14.2014

Sidaros, A., Engberg, A.W., Sidaros, K., Liptrot, M.G., Herning, M., Petersen, P., Paulson, O.B., Jernigan, T.L. and Rostrup, E., 2008. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. Brain, 131(2), pp.559-572. https://doi.org/10.1093/brain/awm294

Slattery, C.F., Zhang, J., Paterson, R.W., Foulkes, A.J.M., Carton, A., Macpherson, K., Mancini, L., Thomas, D.L., Modat, M., Toussaint, N., Cash, D.M., Thornton, J.S., Henley, S.M.D., Crutch, S.J., Alexander, D.C., Ourselin, S., Fox, N.C., Zhang, H., Schott, J.M., 2017. ApoE influences regional white-matter axonal density loss in Alzheimer's disease. Neurobiology of aging 57, 8–17. https://doi.org/10.1016/j.neurobiolaging.2017.04.021

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M. and Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage, 31(4), pp.1487-1505. https://doi.org/10.1016/j.neuroimage.2006.02.024

Smith, S.M. and Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage, 44(1), pp.83-98. https://doi.org/10.1016/j.neuroimage.2008.03.061

Smith, E.E., Salat, D.H., Jeng, J., McCreary, C.R., Fischl, B., Schmahmann, J.D., Dickerson, B.C., Viswanathan, A., Albert, M.S., Blacker, D. and Greenberg, S.M., 2011. Correlations

between MRI white matter lesion location and executive function and episodic memory. Neurology, 76(17), pp.1492-1499. https://doi.org/ 10.1212/WNL.0b013e318217e7c8

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E. and Niazy, R.K., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage, 23, pp.S208-S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Spreng, R.N., Shoemaker, L. and Turner, G.R., 2017. Executive functions and neurocognitive aging. In Executive functions in health and disease (pp. 169-196). Academic Press. https://doi.org/10.1016/B978-0-12-803676-1.00008-8

Stotesbury, H., Kirkham, F.J., Kölbel, M., Balfour, P., Clayden, J.D., Sahota, S., Sakaria, S., Saunders, D.E., Howard, J., Kesse-Adu, R. and Inusa, B., 2018. White matter integrity and processing speed in sickle cell anemia. Neurology, 90(23), pp. e2042-e2050. https://doi.org/10.1212/WNL.0000000000005644

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. Journal of experimental psychology, 18(6), 643–662. https://doi.org/10.1037/h0054651

Sturm, W., Willmes, K., & Horn, W. (1993). Leistungsprüfungssystem für 50-90 jährige. Handanweisung (2nd ed.). Göttingen: Hogrefe.

Sullivan, E.V. and Pfefferbaum, A., 2006. Diffusion tensor imaging and aging. Neuroscience & Biobehavioral Reviews, 30(6), pp.749-761. https://doi.org/10.1016/j.neubiorev.2006.06.002

Sullivan, E.V., Rohlfing, T. and Pfefferbaum, A., 2010a. Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. Developmental neuropsychology, 35(3), pp.233-256. https://doi.org/10.1080/87565641003689556

Sullivan, E.V., Rohlfing, T. and Pfefferbaum, A., 2010b. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed

performance. Neurobiology of aging, 31(3), pp.464-481. https://doi.org/10.1016/j.neurobiolaging.2008.04.007

Sullivan, E.V., Zahr, N.M., Rohlfing, T. and Pfefferbaum, A., 2010. Fiber tracking functionally distinct components of the internal capsule. Neuropsychologia, 48(14), pp.4155-4163. https://doi.org/10.1016/j.neuropsychologia.2010.10.023

Tabachnick, B.G. and Fidell, L.S., 2007. Multivariate analysis of variance and covariance. Using multivariate statistics, 3, pp.402-407.

Timmers, I., Roebroeck, A., Bastiani, M., Jansma, B., Rubio-Gozalbo, E. and Zhang, H., 2016. Assessing microstructural substrates of white matter abnormalities: a comparative study using DTI and NODDI. PloS one, 11(12), p.e0167884. https://doi.org/10.1371/journal.pone.0167884

United Nations, Department of Economic and Social Affairs, Population Division. World Population Ageing 2017 - Highlights (ST/ESA/SER.A/397). 2017:1.

Verdelho, A., Madureira, S., Ferro, J.M., Basile, A.M., Chabriat, H., Erkinjuntti, T., Fazekas, F., Hennerici, M., O'Brien, J., Pantoni, L. and Salvadori, E., 2007. Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. Journal of neurology, neurosurgery & psychiatry, 78(12), pp.1325-1330. https://doi.org/10.1136/jnnp.2006.110361

Vernooij, M.W., Ikram, M.A., Vrooman, H.A., Wielopolski, P.A., Krestin, G.P., Hofman, A., Niessen, W.J., Van der Lugt, A. and Breteler, M.M., 2009. White matter microstructural integrity and cognitive function in a general elderly population. Archives of general psychiatry, 66(5), pp.545-553. https://doi.org/10.1001/archgenpsychiatry.2009.5

Vidal-Pineiro, D., Wang, Y., Krogsrud, S.K., Amlien, I.K., Baaré, W.F., Bartres-Faz, D., Bertram, L., Brandmaier, A.M., Drevon, C.A., Düzel, S. and Ebmeier, K., 2021. Individual variations in 'brain age'relate to early-life factors more than to longitudinal brain change. Elife, 10, p.e69995. https://doi.org/10.7554/eLife.69995

Voineskos, A.N., Rajji, T.K., Lobaugh, N.J., Miranda, D., Shenton, M.E., Kennedy, J.L., Pollock, B.G. and Mulsant, B.H., 2012. Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. Neurobiology of aging, 33(1), pp.21-34. https://doi.org/10.1016/j.neurobiolaging.2010.02.009

Walhovd, K.B., Johansen-Berg, H. and Karadottir, R.T., 2014. Unraveling the secrets of white matter–bridging the gap between cellular, animal and human imaging studies. Neuroscience, 276, pp.2-13. https://doi.org/10.1016/j.neuroscience.2014.06.058

Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M. and Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage, 92, pp.381-397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Westlye, L.T., Walhovd, K.B., Dale, A.M., Bjørnerud, A., Due-Tønnessen, P., Engvig, A., Grydeland, H., Tamnes, C.K., Østby, Y. and Fjell, A.M., 2010. Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. Cerebral cortex, 20(9), pp.2055-2068. https://doi.org/10.1093/cercor/bhp280

Winston, G.P., 2012. The physical and biological basis of quantitative parameters derived from diffusion MRI. Quantitative imaging in medicine and surgery, 2(4), p.254. https://doi.org/ 10.3978/j.issn.2223-4292.2012.12.05

Xie, S., Zhang, Z., Chang, F., Wang, Y., Zhang, Z., Zhou, Z. and Guo, H., 2016. Subcortical white matter changes with normal aging detected by multi-shot high resolution diffusion tensor imaging. PLoS One, 11(6), p.e0157533. https://doi.org/10.1371/journal.pone.0157533

Yendiki, A., Koldewyn, K., Kakunoori, S., Kanwisher, N. and Fischl, B., 2014. Spurious group differences due to head motion in a diffusion MRI study. Neuroimage, 88, pp.79-90. https://doi.org/10.1016/j.neuroimage.2013.11.027

Yoon, B., Shim, Y.S., Lee, K.S., Shon, Y.M. and Yang, D.W., 2008. Region-specific changes of cerebral white matter during normal aging: a diffusion-tensor analysis. Archives of gerontology and geriatrics, 47(1), pp.129-138. https://doi.org/10.1016/j.archger.2007.07.004

Yu, J., Lee, T.M. and Frontotemporal Lobar Degeneration Neuroimaging Initiative, 2019. The longitudinal decline of white matter microstructural integrity in behavioral variant frontotemporal dementia and its association with executive function. Neurobiology of aging, 76, pp.62-70. https://doi.org/10.1016/j.neurobiolaging.2018.12.005

Zhang, H., Schneider, T., Wheeler-Kingshott, C.A. and Alexander, D.C., 2012. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage, 61(4), pp.1000-1016. https://doi.org/10.1016/j.neuroimage.2012.03.07

Zhang, H., Avants, B.B., Yushkevich, P.A., Woo, J.H., Wang, S., McCluskey, L.F., Elman, L.B., Melhem, E.R. and Gee, J.C., 2007. High-dimensional spatial normalization of diffusion tensor images improves the detection of white matter differences: an example study using amyotrophic lateral sclerosis. IEEE transactions on medical imaging, *26*(11), pp.1585-1597. https://doi.org/ 10.1109/TMI.2007.906784

Zhang, H., Yushkevich, P.A., Rueckert, D. and Gee, J.C., 2010, July. A computational white matter atlas for aging with surface-based representation of fasciculi. In International Workshop on Biomedical Image Registration (pp. 83-90). Springer, Berlin, Heidelberg

Zhang, H., Yushkevich, P.A., Alexander, D.C. and Gee, J.C., 2006. Deformable registration of diffusion tensor MR images with explicit orientation optimization. Medical image analysis, 10(5), pp.764-785. https://doi.org/10.1016/j.media.2006.06.004

Zheng, Z., Shemmassian, S., Wijekoon, C., Kim, W., Bookheimer, S.Y. and Pouratian, N., 2014. DTI correlates of distinct cognitive impairments in Parkinson's disease. Human brain mapping, 35(4), pp.1325-1333. https://doi.org/10.1002/hbm.22256

6 Appendix

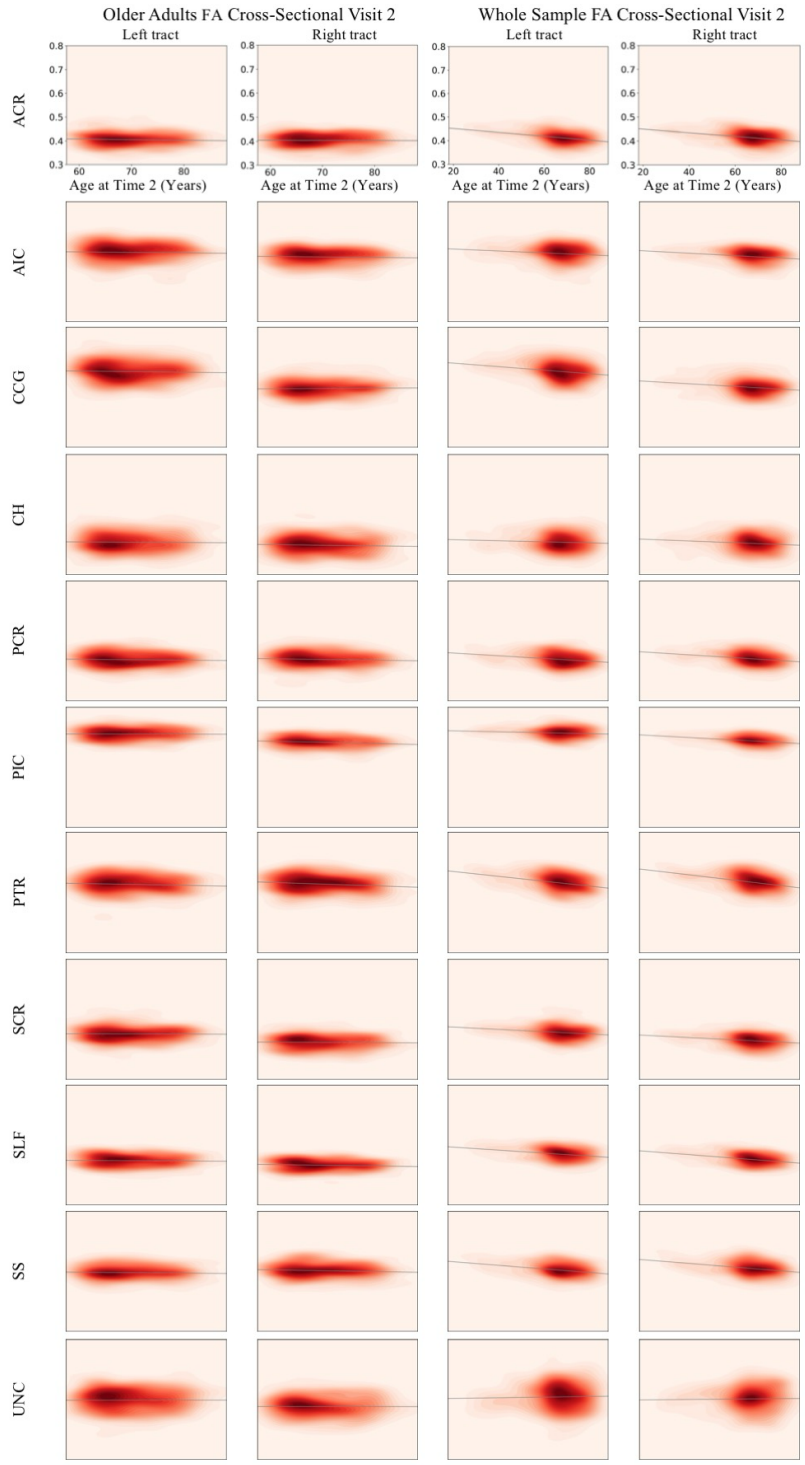

Fig. 7: Cross-sectional tract mean FA values at second visit plotted against age in older adults and in young to older adults (whole sample). Darker areas of the kernel density plots show greater degree of data point overlap. Key: ACR, anterior corona radiata; AIC, anterior limb of the internal capsule; CCG, cingulum at the cingulate gyrus area; CH, cingulum at the hippocampus area; PCR, posterior corona radiata; PIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SS, sagittal stratum; UNC, uncinate fasciculus.

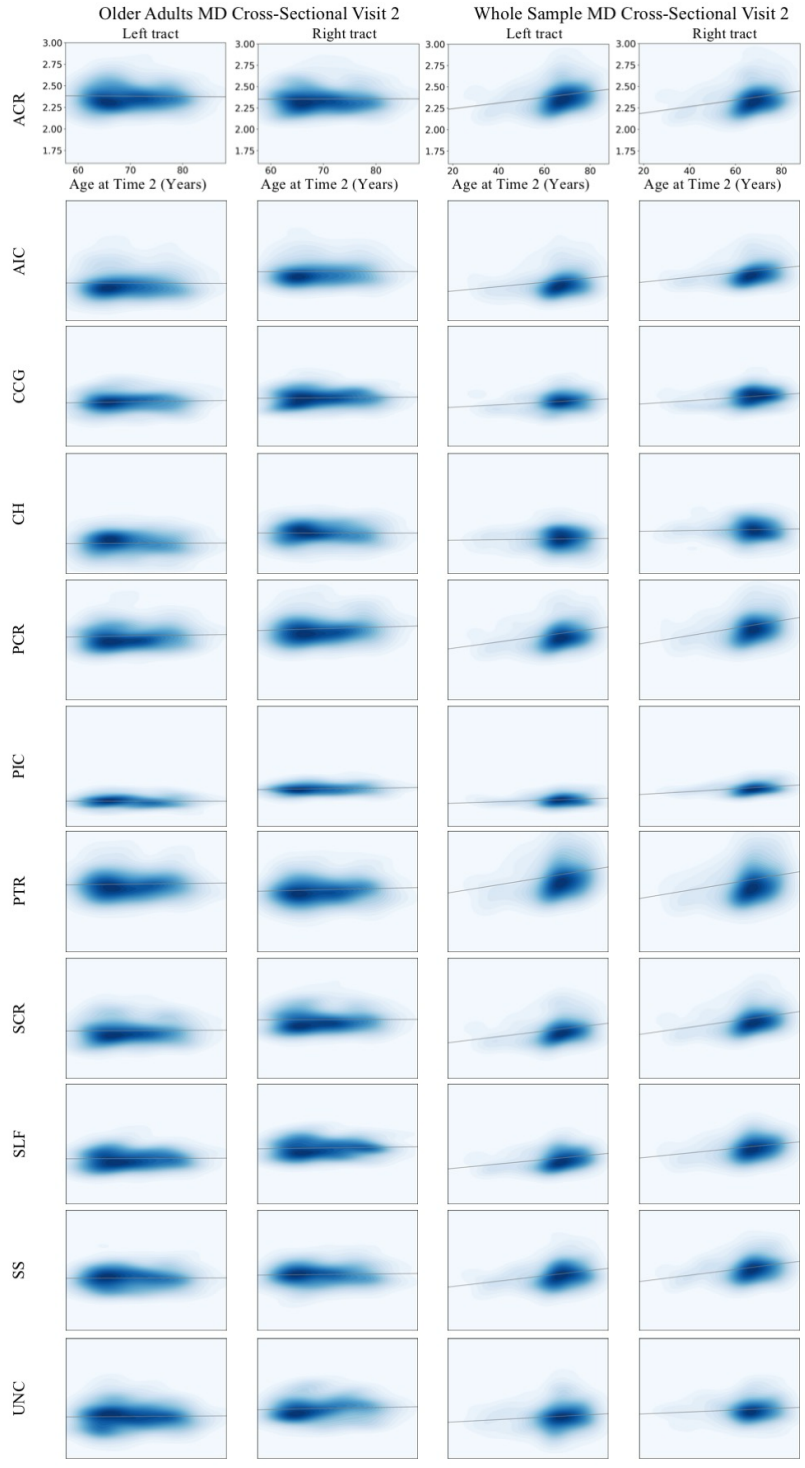

Fig. 8: Cross-sectional tract mean MD values at second visit plotted against age in older adults and in young to older adults (whole sample). Darker areas of the kernel density plots show greater degree of data point overlap. Key: ACR, anterior corona radiata; AIC, anterior limb of the internal capsule; CCG, cingulum at the cingulate gyrus area; CH, cingulum at the hippocampus area; PCR, posterior corona radiata; PIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SS, sagittal stratum; UNC, uncinate fasciculus.

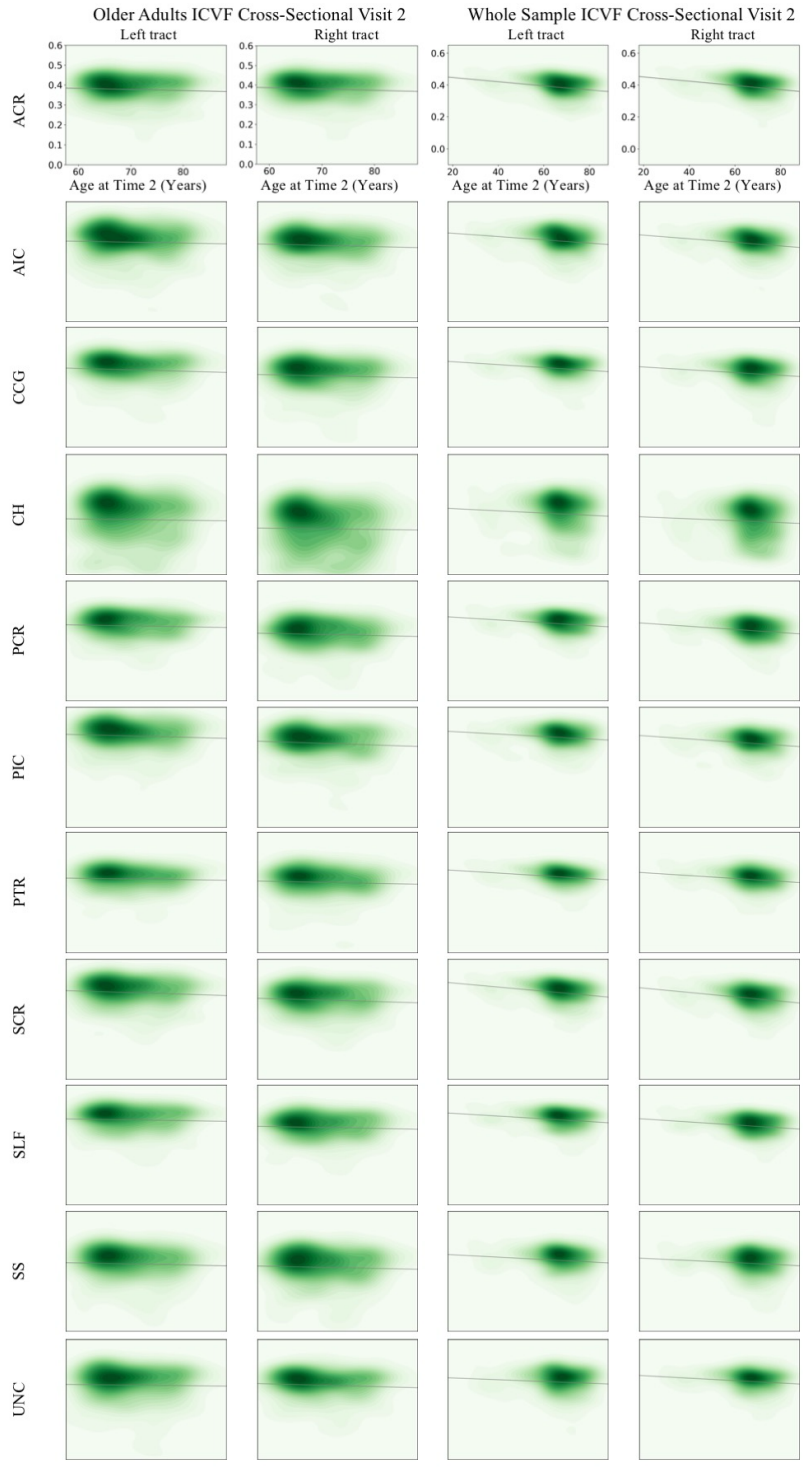

Fig. 9: Cross-sectional tract mean ICVF values at second visit plotted against age in older adults and in young to older adults (whole sample). Darker areas of the kernel density plots show greater degree of data point overlap. Key: ACR, anterior corona radiata; AIC, anterior limb of the internal capsule; CCG, cingulum at the cingulate gyrus area; CH, cingulum at the hippocampus area; PCR, posterior corona radiata; PIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SS, sagittal stratum; UNC, uncinate fasciculus.

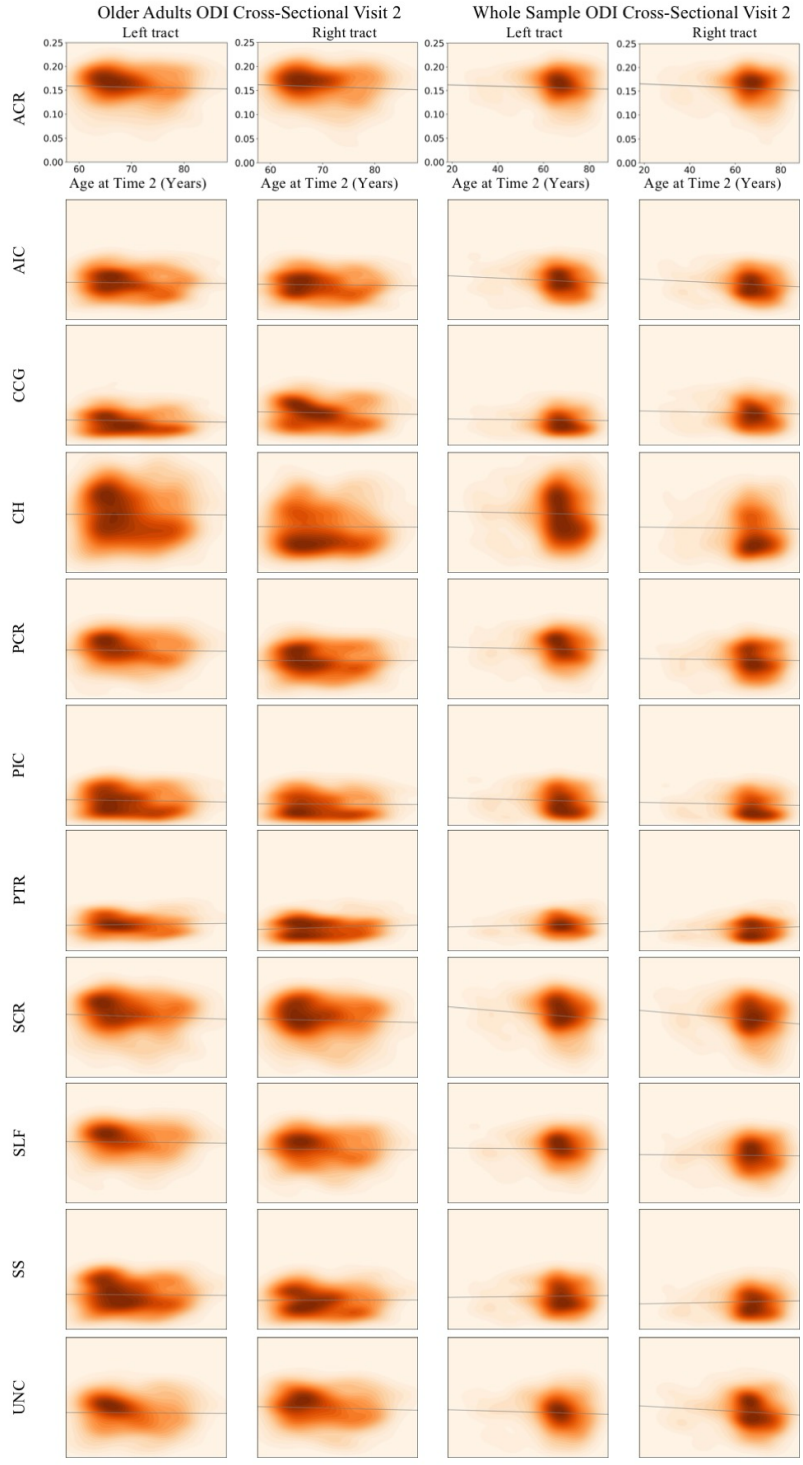

Fig. 10: Cross-sectional tract mean MD values at second visit plotted against age in older adults and in young to older adults (whole sample). Darker areas of the kernel density plots show greater degree of data point overlap. Key: ACR, anterior corona radiata; AIC, anterior limb of the internal capsule; CCG, cingulum at the cingulate gyrus area; CH, cingulum at the hippocampus area; PCR, posterior corona radiata; PIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SS, sagittal stratum; UNC, uncinate fasciculus.

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