

École polytechnique de Louvain

Using cingulum bundle microstructural models metrics to better understand the early posterior cingulate hypometabolism in the framework of Alzheimer's Disease

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Abstract

The increase in the number of elderly people in our society has led to a higher occurrence of aging-related illnesses such as Alzheimer's disease. A novel approach has yielded the identification of fresh biomarkers that hold potential for enhancing diagnoses, personalized treatment, clinical management, and drug development. Utilizing diffusion magnetic resonance imaging, a non-invasive imaging technique devoid of invasive procedures or radiation, it becomes possible to assess the microstructural attributes of brain tissues by examining the diffusion of water molecules across biological barriers. This process of linking the diffusion magnetic resonance signal to tissue microstructural characteristics through mathematical models is termed "microstructure imaging." This Master's thesis seeks to explore the hypometabolism within the posterior cingulate in the context of Alzheimer's disease using the accumulation of biomarkers and microstructural metrics originating from models such as Diffusion Tensor Imaging (DTI), Neurite Orientation Dispersion and Density Imaging (NODDI), Distribution of 3D Anisotropic Microstructural Environments in Diffusion compartment imaging (DIAMOND), and Microstructure Fingerprinting (MF).

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Acronyms

AD Alzheimer's Disease.

AD-P AD-pathophysiological process.

ADAD autosomal dominant AD.

ADC Apparent Diffusion Coefficient.

APOE Apolipoprotein E.

APP Amyloid Precursor Protein.

AxD Axial Diffusivity.

CSF Cerebrospinal fluid.

DIAMOND Distribution of 3D Anisotropic Microstructural Environments in Diffusion compartment imaging.

DICOM Digital Imaging and Communications in Medicine.

dMRI diffusion Magnetic Resonance Imaging.

DTI Diffusion Tensor Imaging.

DW-MRI Diffusion-Weighted Magnetic Resonance Imaging.

EOAD early-onset AD.

FA Fractional Anisotropy.

FCSRT Free and Cued Selective Reminding Test.

FDG Fluorodésoxyglucose.

fextra extracellular volume fraction.

fintra intracellular volume fraction.

fiso free water volume fraction.

fMRI functional MRI.

FOV Field of View.

fvf_tot total fiber volume fraction.

HCB Hippocampal Cingulum Bundle.

HCP1065 Human Connectome Project 1065.

LOAD late-onset AD.

MCI Mild Cognitive Impairment.

MD Mean Diffusivity.

MF Microstructure Fingerprinting.

MMSE Mini-Mental State Examination.

MNI152 Montreal Neurological Institute 152.

MPPCA Marchenko-Pastur Principal Component Analysis.

MRI Magnetic Resonance Imaging.

MTL Medial Temporal Lobe.

Nifti Neuroimaging Informatics Technology Initiative.

NODDI Neurite Orientation Dispersion and Density Imaging.

ODI Orientation Dispersion Index.

PCC Posterior Cingulate Cortex.

PET Positron Emission Tomography.

RD Radial Diffusivity.

RF Radio Frequency.

RGB Red Green Blue.

ROI Region Of Interest.

TE Echo Time.

TR Repetition Time.

UF Uncinate Fasciculus.

wAxD weighted Axial Diffusivity.

wFA weighted Fractional Anisotropy.

wfvf weighted fiber volume fraction.

WM White Matter.

wMD weighted Mean Diffusivity.

wRD weighted Radial Diffusivity.

Introduction

The increase in the number of elderly people in our society has led to a higher occurrence of aging-related illnesses such as Alzheimer's Disease (AD). Dementia, which is an advanced stage of AD characterized by memory loss and behavioral symptoms impacting daily life, affected over 52 million people worldwide in 2020 and 212,000 in Belgium in 2018 [1]. This neurodegenerative disease is a major concern in today's society because there is currently no pharmacological treatment available to prevent or halt its progression. However, researchers are actively investigating the underlying mechanisms to better understand the disease. Recently, there has been a shift towards defining the disorder based on its biological neuropathological hallmarks instead of just clinical symptoms. This new approach has led to the discovery of new biomarkers that could improve diagnosis, personalized treatment, clinical management, and drug development [2].

DW-MRI is a type of imaging that doesn't involve invasive procedures or radiation, and it's used to evaluate the microstructural characteristics of tissues in the brain by examining how water molecules diffuse through biological barriers. The process of connecting the diffusion magnetic resonance signal to the microstructural properties of tissues using mathematical models is referred to as "microstructure imaging". By using this technique, it's possible to identify microstructural changes that occur years before symptoms appear, making it a valuable tool in identifying biomarkers that can distinguish between normal and pathological cases with high reliability. These biomarkers can offer specific and sensitive insights into the early stages of the disease and the underlying biological mechanisms involved.

The objective of this Master's thesis is to investigate the hypometabolism in the posterior cingulate in the context of Alzheimer's disease using microstructural metrics and biomarkers accumulation. The first chapter is divided into two sections: the first section provides a theoretical understanding of DW-MRI and the various diffusion models utilized in this study, including Diffusion Tensor Imaging (DTI), Neurite Orientation Dispersion and Density Imaging (NODDI), Distribution of 3D Anisotropic Microstructural Environments in Diffusion compartment imaging

(DIAMOND), and Microstructure Fingerprinting (MF). The second section of this chapter presents the biological processes associated with AD, different stages of the disease, and current diagnostic biomarkers. The chapter also delves into the results of previous studies that utilized diffusion models to characterize microstructural changes in individuals with dementia, mild cognitive impairment (MCI), and healthy elderly, which provides the necessary background to understand why this master thesis try to explain the hypometabolism in the posterior cingulate. The second chapter explain the methods of this study, then it show the results and discuss the association between the cingulum bundle connectivity and the posterior cingulate metabolism to answer the question of research. Finally, the limitations of this study are addressed as well as further perspectives for the future.

Chapter 1

State of the Art

1.1 diffusion Magnetic Resonance Imaging (dMRI)

1.1.1 Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI)

Diffusion-Weighted Magnetic Resonance Imaging aims to highlight microscopic movements of water in tissues. Indeed, molecules of water are not immobile in a biological medium. They are subject to permanent agitation called Brownian motion. These movements are randoms and more or less intense according to the medium. They characterize the diffusion, the freer the water is in an area, the easier the movements and higher the diffusion. On the contrary, in some parts of the tissues, the agitation is reduced because of obstacles opposing these movements. In MRI, in the presence of a magnetic field gradient, the movements of hydrogen protons lead to dephases and thus are responsible for a decrease in the signal. These decreases are more important if the movements of protons are fast. The agitation of water molecules will therefore have effects on the signal. With standard sequences, the loss of signal is hard to see. To highlight these microscopic molecular movements and to obtain weighted images in diffusion, we add additional gradients in an echo planar spin echo sequence. These diffusion gradients are applied before and after the 180° RF impulsion. The dephasing provoked by the first gradient for immobile protons is perfectly compensated by the second gradient. Therefore the signal of immobile water molecules is not decreased. On the other side, the mobile protons are dephasing faster during the first gradient application and this dephasing is not compensated by the second one. This is why the signal decreases. This decrease is even more important the faster the molecular movements are. The diffusion effect depends on the performance of the gradients. It is characterized by

a gradient factor called "b" which is determined with the following relation :

$$b = (\gamma G \tau)^2 (T - \tau/3) \quad (1.1)$$

where γ is the gyromagnetic ratio, G is the amplitude of the gradient, τ the duration of the application of the gradient, and T is the time between the application of both gradients of diffusion. b is expressed in $[s/mm^2]$ and can varies between 0 and 5000 $[s/mm^2]$ or even higher. Increasing the b-value, increases the sensibility of the sequence to the molecular diffusion phenomena. Three diffusion gradients are applied following the three axes : x, y and z, yielding three resultant images. Since diffusion-weighted images exhibit a hypersignal in areas with diminished molecular diffusion, a fourth image is constructed through a composite of the preceding three images. This processing consists of averaging each pixel from the three diffusion images and keeping the hypersignal only if it is present in the three axes. Thus, on the diffusion image obtained, a hypersignal will correspond to a decrease in diffusion in the three directions. For example, this fourth image is important to analyse the white matter of the brain. Indeed a hypersignal can mean a perpendicular arrangement of white matter fibers with respect to the diffusing gradient [3].

Another measurable parameter is the Apparent Diffusion Coefficient (ADC). It allows to evaluate with precision the anomalies in diffusion. The attenuation of the signal bonded to the diffusion phenomena of water molecules is characterized by the relation :

$$Att = e^{(-b*ADC)} \quad (1.2)$$

where b is the gradient factor seen above and ADC is the coefficient of apparent diffusion. It is expressed in $[mm^2/s]$. To calculate the ADC, two acquisitions are required : one without diffusion gradient ($b = 0$) which gives a signal S_0 and one acquisition with gradients of diffusion with a determined value for b that gives a signal S . Therefore we can obtain the value of ADC with the relation 1.3 and calculate the ADC for different biological tissue :

$$\log(S/S_0) = -b * ADC. \quad (1.3)$$

1.1.2 Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging uses a tensor to define the diffusion. It allows to extract diffusion anisotropy effect from MRI. This diffusion tensor is define as follows :

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}. \quad (1.4)$$

The diagonal elements of the tensor represent the variances of diffusion along the x, y, and z axes, while the off-diagonal elements represent the covariances between these axes and are symmetric about the diagonal. Therefore only six noncollinear diffusion encoding directions are required to measure the tensor.

The tensor can be diagonalized to obtain eigenvalues (λ_1 , λ_2 and λ_3) and eigenvectors (ϵ_1 , ϵ_2 and ϵ_3) describing the directions and apparent diffusivities along the principal axes of diffusion. The tensor can be visualized as an ellipsoid with the eigenvectors defining the principal axes and the radii defined by the eigenvalues on the figure 1.1. When the eigenvalues are similar, diffusion is considered isotropic,

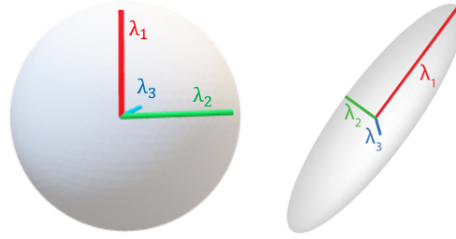


Figure 1.1: Isotropic diffusion on the left and anisotropic diffusion on the right.

while significantly different eigenvalues indicate anisotropic diffusion. Changes in tissue microstructure due to injury, disease, or normal physiological changes can affect the magnitudes of the eigenvalues.

Several metrics can be calculated from the eigenvalues of this tensor :

1. **Mean Diffusivity (MD)** : It is a measure of the magnitude of overall water diffusion in each voxel. It is the average of three eigenvalues :

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}. \quad (1.5)$$

It is an indicator of white matter damage.

2. **Radial Diffusivity (RD)** : It represents the diffusivity along the perpendicular direction of the principal axis of the diffusion ellipsoid. It demonstrates more specific relationships to white matter pathology. It may reflect myelin disruption. It is expressed as follows :

$$RD = \frac{\lambda_2 + \lambda_3}{2}. \quad (1.6)$$

3. **Axial Diffusivity (AxD)** : It represents the diffusivity along the principal axis of the diffusion ellipsoid and is more specific to axonal degeneration or deletion and is expressed as :

$$AxD = \lambda_1. \quad (1.7)$$

4. **Fractional Anisotropy (FA)** : It measures the degree of diffusion anisotropy and is defined as follows :

$$FA = \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}. \quad (1.8)$$

It is a useful measure because it ranges from 0 (indicating isotropic diffusion) to 1 (indicating anisotropic diffusion), providing a convenient way to quantify the degree of anisotropy. A value of 0 is obtained when diffusion is isotropic, with all eigenvalues ($\lambda_1 = \lambda_2 = \lambda_3$) being equal. On the other hand, a FA value close to 1 suggests a high degree of anisotropy in the diffusion process. It is an indirect indicator of axonal integrity and an indicator of packing of fibers in a voxel.

From these measures we can create maps as on figure 1.2.

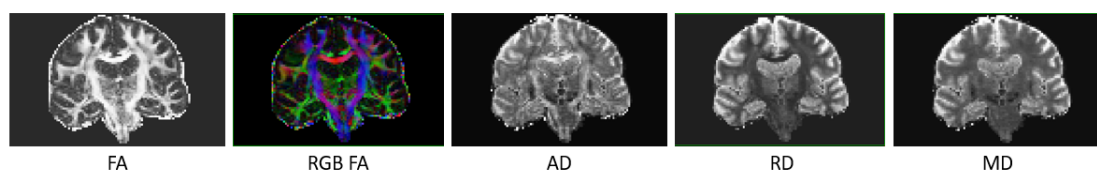


Figure 1.2: Coronal slice of maps from patient 9. From left to right : the FA followed by the RGB FA, the AxD, the RD and finally the MD map.

In addition to these scalar measures, we can also visualize orientation information. A color-coded orientation map of the major eigenvector is one method to visualize orientation information, in which red, green, and blue colors are assigned to right-left, anterior-posterior, and superior-inferior orientations, respectively. Indeed, within the brain, water diffusion tends to be more anisotropic in white matter regions, while being isotropic in CSF and almost isotropic in gray matter. In regions of homogeneous white matter, the primary eigenvector of diffusion (representing the direction of greatest diffusivity) is assumed to align with the orientation of nerve fiber tracts. This relationship forms the foundation for using tractography algorithms to estimate the trajectories of white matter pathways [4].

Limitations of DTI

While DTI is widely used for both basic and clinical research purposes, there are two main limitations that should be taken into account. Firstly, water diffusion is an indirect measure of underlying neuroanatomy, and there are many microscopic structures influencing diffusion, leading to similar alterations in DTI-derived parameters despite different histopathological conditions. Secondly, the diffusion process is averaged over a relatively large voxel volume, typically with 2-3 mm resolution, which limits the sensitivity of DTI to the macroscopic configuration of fiber bundles. This makes it difficult to determine whether changes in diffusion are due to alterations at the cellular level or macroscopic reorganization of fiber structures. Indeed fiber populations are sometimes crossing each other which lead to misinterpretations [5].

1.1.3 Neurite Orientation Dispersion and Density Imaging (NODDI)

DTI has been a widely used method to characterize the brain microstructure but other model has been developed like Neurite Orientation Dispersion and Density Imaging (NODDI). Indeed, neurons are composed of projections known as dendrites and axons, collectively called neurites, which form the basis of brain circuitry. Measuring the density and orientation distribution of neurites provides valuable information about the brain's structural foundation and its function in normal and abnormal conditions. For example, the branching complexity of the dendritic trees, measured in terms of dendritic density, reflects the nature of their computation and hence their function: the areas of the cortex with less complex dendritic structures engage in the early stages of information processing while the regions with more complex dendritic structures participate in the later stages of processing. Changes in neurite morphology are also associated with brain development, aging, and various neurological disorders, such as Alzheimer's disease and multiple sclerosis. NODDI will therefore capture the key features of neurite morphology [6].

NODDI distinguishes three types of microstructural environment : intra-cellular (ic), extra-cellular (ec) and the CSF (iso) compartment. Each affects water diffusion in a unique way and therefore gives rise to a separate normalized MR signal. The signal A can be written as :

$$A = (1 - \nu_{iso})(\nu_{ic}A_{ic} + (1 - \nu_{ic})A_{ec}) + \nu_{iso}A_{iso} \quad (1.9)$$

where A and ν are the normalized signal and volume fraction of respective compartment. [6].

First, the intra-cellular compartment refers to the space bounded by the membranes of neurites. This space is modeled as a set of sticks which are cylinders of zero radius. These sticks capture the restricted nature of diffusion perpendicular to neurites and unhindered diffusion along them. The orientation distribution of sticks can range from highly parallel to highly dispersed, which reflects the spectrum of neurite orientation patterns observed in brain tissue. The fraction of voxel occupied by this compartment is named *fintra* which characterizes the way the fiber volume evolves. In cases where the value of *fintra* increases in the white matter, it could indicate one of two possibilities: either the proportion of fibers in the area being examined has increased, suggesting axonal regrowth, or the volume of fibers has increased due to axonal swelling, indicating inflammation in the white matter. Conversely, if *fintra* decreases, it could be due to a decrease in either the proportion or volume of fibers, which may be a result of inflammation in the extra-axonal space or axonal degeneration/deletion.

Secondly, the extra-cellular compartment refers to the space around the neurites. In this space, there are various types of glial cells and, additionally in gray matter, cell bodies. The diffusion of water molecules is hindered by the presence of neurites but not restricted. Thus it is modeled with simple anisotropic diffusion. The fraction in a voxel that is taken up by the extracellular compartment is called *fextra*. When *fextra* is high, it can indicate a higher quality of the myelin sheath or swelling of the extra-axonal cells caused by inflammation.

Finally, the CSF compartment refers to the space occupied by cerebrospinal fluid and is modeled as isotropic Gaussian diffusion. The fraction in a voxel is called *fiso* which refers in reality to a compartment characterized by a fully isotropic diffusion.

Another metric which can be considered is the Orientation Dispersion Index (*ODI*). It ranges from 0 to 1, while 0 represents fully aligned fibers, 1 represents fully isotropic structure. In white matter, an increase of *ODI* means more fiber dispersion while a decrease reflects axonal packing [6].

1.1.4 Distribution of 3D Anisotropic Microstructural Environments in Diffusion compartment imaging (DIAMOND)

The NODDI model explicitly models the dispersion of fascicles in each voxel using a Watson distribution of sticks. However, this comes at a cost of several key assumptions that are not consistent with the known tissue microstructure. The

model assumes a fixed representation of a white matter fascicle constant throughout the entire brain, despite the fact that fascicles with various microstructures have been observed. Additionally, NODDI, similarly to DTI does not account for intra-axonal radial diffusivity and only considers a single fascicle compartment per voxel, even though fascicles crossing with angles greater than 40 degrees occur in 60 to 90% of the voxels in the human brain. While NODDI may capture crossing fascicles as increased dispersion, it cannot characterize each of them separately. To address these limitations, 3D spin-packets are considered so that when interacting with an homogeneous portion of the microstructure they give rise to anisotropic 3D Gaussian diffusion represented by a diffusion tensor D . This enables to capture the local 3D structure of the restriction and hindrance to diffusion of water molecules. Spin packets travel along different trajectories and are confronted with different barriers to displacement. Therefore the DW signal S_k is modeled like this :

$$S_k = S_0 \int P(D) e^{-b_k g_k^T D g_k} dD \quad (1.10)$$

where b_k is the b-value, S_0 is the signal with no diffusion applied, g_k is the diffusion gradient and $P(D)$ is a matrix-variate probability distribution that describes the fraction of spin packets given the diffusion tensor D [7].

If a voxel consists of exactly one homogeneous microstructural environment characterized by a tensor D^0 , $P(D)$ would be a delta function $P(D) = \delta(D - D^0)$ and the model would be equivalent to DTI. However, in reality it contains compartment and each compartment is not entirely homogeneous and requires a population of spin packets to describe its heterogeneity. This can be achieved by modeling each compartment's composition using the matrix-variate Gamma ($mv - \Gamma$) distribution that is defined as follows:

$$P_{\kappa, \Sigma}(D) = \frac{|D|^{\kappa - (p+1)/2}}{|\Sigma|^{\kappa} \Gamma_p(\kappa)} e^{-\text{trace}(\Sigma^{-1} D)} \quad (1.11)$$

$$\Gamma_p(\kappa) = \pi^{p(p-1)/4} \prod_{j=1}^p \Gamma(\kappa - (j-1)/2) \quad (1.12)$$

with the shape parameter κ to capture the heterogeneity of the spin packet population, with P being the scale parameter and $\Gamma_p(\kappa)$ being the multivariate Gamma function. A narrow peak of $\Gamma_p(\kappa)$ indicates a more homogeneous population, while a broad peak indicates a more heterogeneous population. This concept can be extended to N_p populations of spin packets in a voxel, with each population characterized by a matrix-variate Gamma distribution $P_{\kappa_j, \Sigma_j}(D)$:

$$P(D) = \sum_{j=1}^{N_p} f_j P_{\kappa_j, \Sigma_j}(D) \quad (1.13)$$

where $f_j \in [0, 1]$ are the fractions of occupancy and their sum is equal to one. This model is represented on figure 1.3 [7].

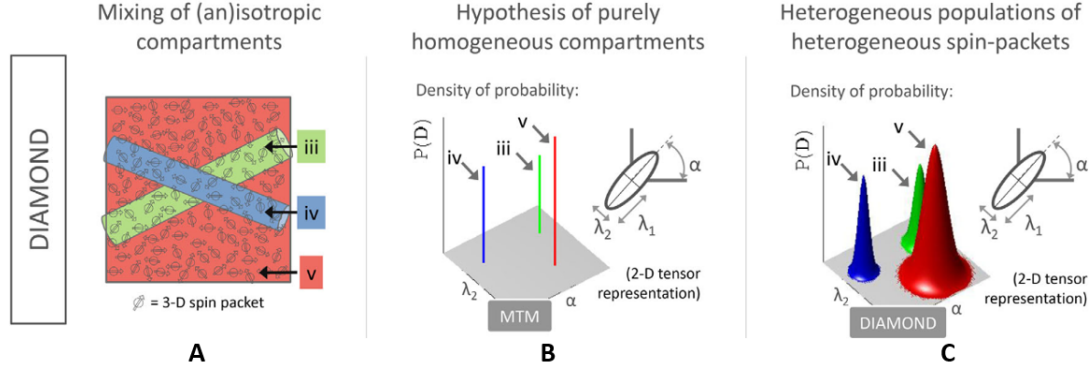


Figure 1.3: DIAMOND model : **A** Multiple compartments, with one isotropic compartment (red) and two anisotropic compartments (blue and green) mixed together. **B** When assuming that the compartments are purely homogeneous and there is no exchange between them, the probability density of diffusivities in this case is a combination of delta functions. **C** DIAMOND is a technique that captures the multidimensional diffusivity and heterogeneity of each compartment using peak-shaped distributions of multidimensional diffusivities.

The DIAMOND method is a versatile approach which can be used to derive various metrics, including FA, MD, AxD and RD, by manipulating its direct outputs. These metrics are referred to as cFA, cMD, cAxD, and cRD to distinguish them from the traditional DTI metrics. DIAMOND also offers a global measure of heterogeneity considering the orientations of fascicles, but this requires defining the number of tissue compartments in each voxel. This voxel-wise compartmentalization is necessary for accurate measurements.

1.1.5 Microstructure Fingerprinting (MF)

The MF multi-compartment model use Monte Carlo simulations to build a dictionary using fingerprints each of which correspond to a unique microstructural configuration. A fingerprint is a set of M gradient profile that are used to make the acquisition of the signal. The dictionary will contain different parameters of the model such as the orientations of the fibers, their density, ... A sparse optimization problem is solved to obtain the right information about the compartment. Then the sum of each information about the signal of each compartment is done using

the principle of superposition [8].

One of the main advantages of Monte Carlo simulations is their ability to generate precise signals for any given tissue geometry. Monte Carlo simulations naturally incorporate physical consistency between the intra- and extra-axonal compartments. This allows to best represents the information contained in the DW-MRI signal [8].

1.2 Alzheimer's disease

1.2.1 Overview of Alzheimer's disease

Alzheimer's disease is the most prevalent type of dementia, affecting millions of people worldwide, with an increasing number of cases. The disease poses a significant social and economic burden. Therefore this is mandatory to understand how this disease is functioning. New imaging technologies have enabled researchers to study the relationship between two major proteins (amyloid- β and tau) in Alzheimer's disease, as well as their effects on cognition and neurodegeneration in humans. It appears that amyloid- β deposition in the medial parietal cortex is the first stage of AD, but tau aggregates in the medial temporal lobe may precede amyloid- β deposition in cognitively healthy older individuals. However, it remains unclear whether tau aggregation in the MTL is the initial stage of AD or a relatively harmless occurrence that can be transformed and spread in the presence of amyloid- β . While there is a strong link between amyloid- β and tau, the latter is actually associated with brain atrophy and hypometabolism, which are both related to cognition. While considerable evidence supports the notion of an interaction between amyloid- β and tau contributing to neurodegeneration and dementia, the precise nature of this interaction remains uncertain. Additionally, the distinctive distribution patterns of amyloid- β and tau within the brain pose further complexities. Furthermore, the existence of instances where neurodegeneration occurs independently of the presence of amyloid- β and tau adds to the challenges that this model faces and necessitates comprehensive explanation [9].

The amyloid- β cascade hypothesis represented on Figure 1.4 adress this challenge. It suggests that amyloid- β is the primary cause of Alzheimer's disease. It proposes that the misfolding of extracellular amyloid- β protein in senile plaques and intracellular misfolded tau protein in neurofibrillary tangles lead to memory loss, confusion, personality changes, and cognitive decline over time [10]. The accumulation of amyloid- β peptide, which derives from the proteolytic cleavage of amyloid precursor protein (APP), is the main component of senile plaques. APP

is a membrane glycoprotein playing a vital role in various biological activities, including neuronal development and signaling. The deposits of amyloid- β peptides are predominantly observed in the hippocampus, neocortex, and cerebrovasculature [11]. This deposit is the inciting event that leads to subsequent downstream processes of tau deposition. The accumulation of tau protein can cause instability in neurons by aggregating and interfering with anterograde and retrograde transport of biomolecules along axons. Tau is a microtubule-associated protein that stabilizes microtubules, which support cellular trafficking and are important for the movement of cargo packages towards and from the perikaryon to the axon and dendrites. The abnormal deposition of modified tau proteins in neurons is a common aspect of many neurodegenerative diseases, known as “tauopathies”. In these diseases, tau aggregates into fibrillary inclusions called neurofibrillary tangles, which cause neuronal death [12].

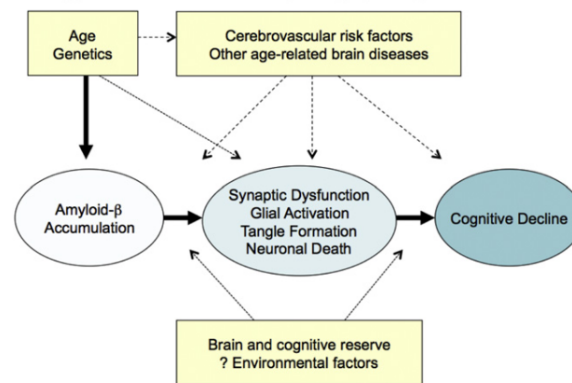


Figure 1.4: Hypothetical model of AD pathophysiological cascade.

1.2.2 Staging of the disease

AD can be divided into three clinical stages :

1. **The preclinical stage**, where no symptoms are observed, but certain biomarkers in the cerebrospinal fluid (CSF) or blood may indicate the earliest signs of AD. Early stages of amyloid- β and tau pathologies are observed during this stage. This stage is due to advancements in the development of in vivo biomarkers that have shifted the diagnosis of Alzheimer's disease from the dementia stage to the prodromal stage, offering the possibility of preclinical diagnosis prior to the onset of symptoms. This has important implications for the evaluation of potential therapies aimed at secondary prevention of Alzheimer's disease. [2]

2. **Mild cognitive impairment (MCI)**. An intermediate stage between normal cognition and dementia; individuals with MCI usually experience amnesia and are at increased risk of developing AD.
3. **Dementia**, characterized by memory loss and behavioral symptoms that interfere with daily activities. The degree of symptoms is correlated with the extent of brain damage.

Individuals with AD can also be differentiated into three widely accepted sub-groups on the basis of their characteristic clinical phenotypes and genetic risks: those with autosomal dominant inheritance (autosomal dominant AD (ADAD)); those with early age at onset, generally before age 65 (early-onset AD (EOAD)); and those with typical late-onset AD (LOAD). Each of these disorders provides a different window into the pathogenesis of AD. LOAD is by far the most common form of AD.

To further explore the preclinical stages of AD, it can be further divided into three stages as depicted on the figure 1.5 [10] :

- **Stage 1: Asymptomatic cerebral amyloidosis stage** These individuals exhibit biomarker evidence of amyloid- β accumulation, but no detectable evidence of additional brain alterations suggesting neurodegeneration or subtle cognitive and/or behavioral symptomatology. The standards for determining "amyloid positivity" are still evolving. Laboratory data increasingly suggest that oligomeric forms of amyloid may play a critical role in the pathological cascade, and work is underway to develop tests for detecting oligomeric forms of amyloid- β in cerebrospinal fluid and plasma. Emerging data from genetically at-risk cohorts also suggest that early synaptic changes may be present before the accumulation of amyloid using currently available amyloid markers. Thus, it may be possible in the future to detect a disease stage preceding stage 1.
- **Stage 2: Amyloid positivity, evidence of synaptic dysfunction and/or early neurodegeneration** These individuals exhibit amyloid positivity and the presence of one or more "downstream" neuronal injury markers related to AD-P. Current markers of neuronal injury are not available. The most validated current markers of neuronal injury include: (1) a high level of tau or phospho-tau in cerebrospinal fluid, (2) hypometabolism in a pattern similar to that of Alzheimer's disease (i.e., in the posterior cingulate cortex, precuneus cortex, and/or temporo-parietal cortex) by FDG-PET, and (3) cortical thinning/gray matter loss in a specific anatomical distribution (i.e., in the lateral and medial parietal cortex, posterior cingulate and lateral temporal

cortex) and/or hippocampal atrophy by volumetric MRI. Future markers may also include fMRI measures of default network connectivity. Although previous studies have shown that on average, amyloid-positive individuals exhibit significantly greater abnormalities on these markers compared to amyloid-negative individuals, there is significant interindividual variability. We assume that amyloid-positive individuals with signs of early neurodegeneration may be further along the trajectory (i.e., at more advanced stages of preclinical AD). It is not yet known whether differences between these other biomarkers of AD-P can be detected, but early synaptic dysfunction, as evaluated by functional imaging techniques such as FDG-PET and fMRI, appears detectable before volumetric loss.

- **Stage 3: Amyloid positivity + evidence of neurodegeneration + subtle cognitive decline** Individuals with biomarkers of amyloid accumulation, early neurodegeneration, and evidence of subtle cognitive decline are at the final stage of preclinical AD and approaching the threshold with proposed clinical criteria for Mild Cognitive Impairment. These individuals may exhibit signs of decline relative to their own reference level especially if accounting for indicators of cognitive reserve, even if their performance remains within the "normal" range of standard cognitive measures. There is emerging evidence that more sensitive cognitive measures, particularly with challenging episodic memory measures, can detect very subtle cognitive impairments in amyloid-positive individuals. It is not yet known whether self-report of memory decline or other subtle neurobehavioral changes will be a useful predictor of progression, but the combination of biomarkers and subjective evaluation of subtle changes may prove useful.

However, the biological definition generates debate regarding its use in daily clinical practice. Indeed, individuals without cognitive impairment may present biomarker evidence of amyloid- β and tau pathology, but often will not develop clinical manifestations during their lifetime. Moreover, this pathology can also be observed in other brain diseases. The limitations of this definition comes from [2]:

- **Risk of confusion between the presence of Alzheimer's brain lesions and Alzheimer's disease :** There is a consensus to dissociate the clinicopathological term "Alzheimer's disease" from neuropathological changes.
- **Low predictive accuracy :** The presence of positivity for both tau protein and beta-amyloid is insufficient to definitively predict the onset of symptoms in individuals without clinical impairment.

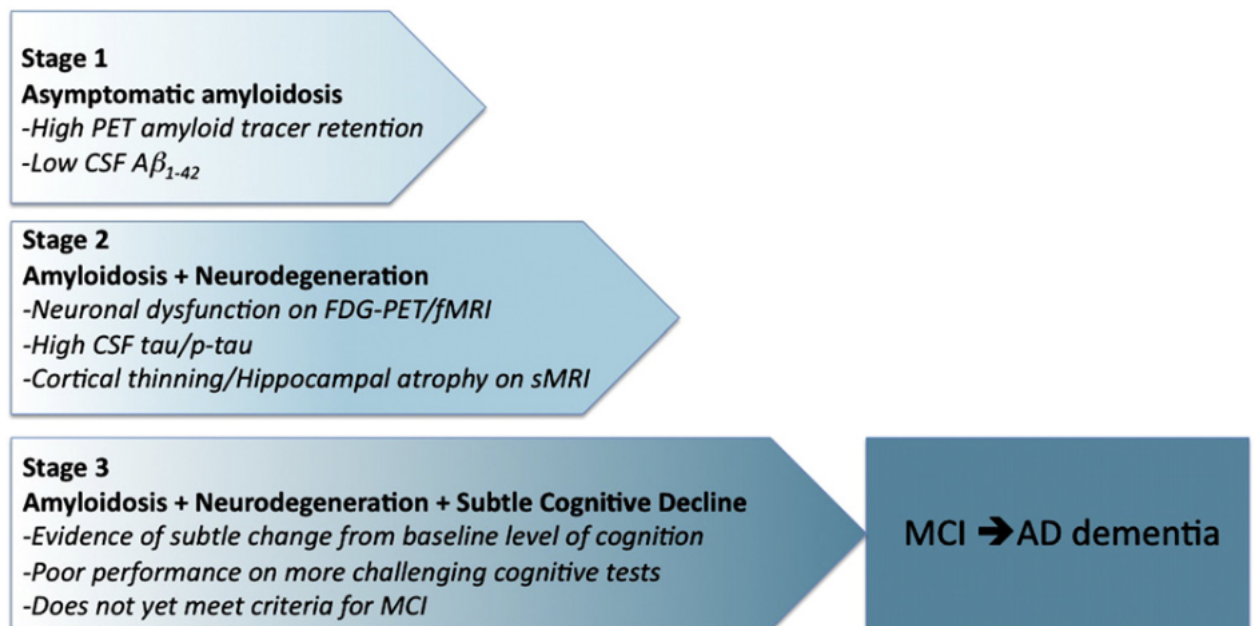


Figure 1.5: Division of the preclinical stages of the AD.

- **Presence of other pathologies :** The in vivo presence of biomarkers for Alzheimer's disease lesions could certify Alzheimer's disease as a primary diagnosis, but such lesions are commonly found in people with other neurodegenerative diseases, most often Lewy body dementia. Patients who exhibit signs of another brain pathology in addition to Alzheimer's lesions should not be considered to have a primary diagnosis of Alzheimer's disease.
- **Uncertainty regarding the pathogenesis model of Alzheimer's disease :** Amyloid- β and tau biomarkers are not sufficient to predict with certainty the progression to symptomatic Alzheimer's disease or Alzheimer's disease dementia, or to define a person's position on the Alzheimer's disease continuum without clinical input.
- **Difficulty in classifying biomarker-positive individuals without cognitive impairment :** People without cognitive impairment who test positive for biomarkers will not invariably experience subsequent cognitive decline.
- **Biomarker thresholds :** A biological diagnosis of Alzheimer's disease based on positive biomarkers requires the need to definitively define positivity thresholds. Any modification of these thresholds would significantly affect the diagnosis and disease stages. The clear separation between negative and positive patients with respect to a given biomarker is somewhat artificial and

differs between sites and studies. Factors contributing to this uncertainty include the specificities of the biomarker used and threshold determination. Moreover, this binary threshold does not reflect the reality of beta-amyloid and tau pathology, which is continuous and present at a minimal degree in almost all people over 70 years old, with important divergences between pathological burden and clinical symptoms at intermediate degrees.

- **Generalizability and accessibility in clinical practice :** The prognostic value of a biomarker-based diagnosis remains limited, firstly because there is great variability in the rate of decline in people with Alzheimer's disease with positive biomarkers, and secondly because other neurodegenerative diseases besides Alzheimer's disease contribute to cognitive decline. Data are even more scarce for people without cognitive impairment, as the currently available models are not suited to the clinical context.
- **Ethical concerns :** Informing people without cognitive impairment that they have an irreversible disease based on biomarkers is an ethical challenge, given that the clinical trajectory towards prodromal Alzheimer's disease or Alzheimer's disease dementia is uncertain, and that there is no way to prevent symptom development in the absence of modifiable risk factors or specific therapies. Alzheimer's disease is one of the most feared diseases, given its consequences, including profound disability and loss of personal dignity. For physicians, Alzheimer's disease is synonymous with neuropathological changes, whereas for patients, Alzheimer's disease is synonymous with dementia, dependence, and death. This profound difference in the use and understanding of the term can harm the therapeutic alliance. In the future, saying that one is at risk of progression, rather than at the preclinical stage of Alzheimer's disease, could facilitate discussions with patients about the risk-benefit balance of any potential treatment and its side effects.

Therefore, Alzheimer's disease should be diagnosed based on both a specific clinical phenotype of Alzheimer's disease and biomarker evidence of Alzheimer's disease pathology. The recommended biomarker measures for amyloid- β pathology are low CSF A β 42, increased CSF A β 40–A β 42 ratio, or high tracer retention in amyloid PET. For tau pathology, high CSF phosphorylated tau or increased ligand retention in tau PET is recommended. In clinical practice, plasma biomarkers for amyloid- β and tau pathology are not currently recommended. The investigation of pathophysiological biomarkers in cognitively unimpaired individuals is not recommended. However, if a biomarker investigation is done in a cognitively unimpaired individual, risk stratification of biomarkers is proposed. Individuals should be counselled before Alzheimer's disease biomarker investigation and should be able to decide whether or not to have the results disclosed to them [2].

1.2.3 Mechanisms and drivers of pathology :

The causes of the AD are still unknown but they are some risk factors that drives the pathology [9].

- **Neural activity :** Brain regions the most metabolically active in youth and maintain this activity throughout adulthood show the greatest deposition of amyloid- β in aging, suggesting a primary role for metabolism in driving amyloid- β deposition. amyloid- β deposition is also associated with increased neural activity evoked by memory encoding in task-positive regions and reduced deactivation in task-negative regions. Moreover, greater activation during memory encoding at baseline predicts subsequent deposition of amyloid- β over the next 4 years. Increased activation during memory encoding is also associated with more tau deposition in the MTL, where both tau and activation may help drive atrophy and cognitive decline. In cognitively healthy individuals with amyloid positivity, low levels of MTL tau pathology are linked to increased functional connectivity, while high levels of tau are associated with decreased connectivity, which could explain connectivity alterations during the progression of disease. Overall, there is a role for increased neural activity in initiating and sustaining amyloid- β accumulation.
- **Networks as facilitators of pathological spread :** The distinct intrinsic connectivity networks in different neurodegenerative disorders are associated with specific patterns of brain atrophy, indicating that certain neural systems are more vulnerable to these diseases. Regional vulnerability and network dysfunction may contribute to the development of neurodegenerative disorders.
- **Apolipoprotein E (APOE) :** It is a polymorphic gene with three alleles; the APOE4 allele is a risk factor for LOAD. The APOE gene polymorphism is associated with the risk of developing AD in all of its clinical forms. Carrying the APOE4 allele increases the deposition of brain amyloid- β in normal aging, as well as at earlier ages.
- **Cerebrovascular disease :** Cerebrovascular disease is known to contribute to the development of dementia, potentially by causing tissue damage and alterations in white matter that increase vulnerability to cognitive dysfunction from other pathological factors like protein aggregation. Nevertheless, there are noteworthy connections between vascular risk factors and both amyloid- β deposition and brain atrophy that tie vascular disease to the molecular mechanisms associated with AD, although more research is needed to fully understand these associations.

- **Environmental factors and lifestyle :** Both cognitive and physical activity have been shown to decrease brain amyloid- β levels in individuals who are cognitively healthy. Greater levels of past and current physical activity are associated with lower levels of brain amyloid- β , especially in individuals who carry the APOE4 allele. Similarly, individuals who report higher levels of cognitive engagement throughout their lives, especially those carrying the APOE4 allele, have also been found to have reduced brain amyloid- β levels. While these findings align with the link between cognitive and physical activity and reduced dementia risk, the mechanisms underlying the direct effects of these factors on amyloid- β remain uncertain. Also poorer sleep quality or less sleep quality could increase brain amyloid- β deposition.
- **Neuroinflammation :** It could be a key event in the pathogenesis of AD but this is unexplained for now.

1.2.4 Literature survey of DW-MRI in Alzheimer's disease

The aim of this section is to examine existing research on the connectivity within regions relevant to this master's thesis within the context of AD. Firstly, a section focuses on DTI and NODDI findings in the WM, specifically the HCB and the UF, among individuals with MCI and AD. Secondly, another section provides an overview of prior investigations regarding the metabolic aspects in the PCC.

DTI and NODDI findings in the WM among MCI and AD individuals

In a study, multishell Diffusion Magnetic Resonance Imaging data were utilized from a cohort of 100 participants, including 40 cognitively normal individuals, 38 with subjective cognitive decline, and 22 with MCI. The objective was to investigate WM alterations in the early stages of AD. The study assessed microstructural degeneration within 27 major tracts of interest using techniques such as DTI, NODDI, and q-space imaging. The outcomes revealed notable patterns, including lower DTI FA values, indicating a decline in organization, and higher RD values, pointing to disruptions in neurobiological barriers and reduced myelination. These changes were particularly evident in the cingulum, thalamic radiation, and forceps major among participants with MCI. Interestingly, these specific tracts also exhibited the strongest predictive capacity for distinguishing between the different groups. Furthermore, the study established a connection between diffusion metrics and cognitive performance, with the most pronounced associations being observed in individuals with MCI. Additionally, the findings brought attention to a heightened ODI in individuals with preclinical AD and MCI in comparison to the healthy control group. These variations indicated a potential "progressed axonal

degeneration and increased axonal bundle disorganization." These alterations in NODDI parameters were predominantly evident in regions such as the left parahippocampal cingulum, the forceps major, and the left posterior thalamic radiation [13].

Mayo et al. conducted a longitudinal study with DTI data from the Alzheimer's Disease Neuroimaging Initiative 2 database. They examined microstructural white matter alterations within groups of individuals with AD and healthy controls, both at baseline and one year later; and microstructural differences between the groups of individuals with AD and healthy controls, assessed at both time points. The results of within-group analysis revealed a widespread decrease in FA and an increase in MD among both individuals with AD and healthy controls. Notably, alterations in the hippocampal cingulum were exclusive to the AD group. In the between-group analysis, relative to the healthy controls, individuals with AD exhibited lower FA and higher MD in various regions, including the hippocampal cingulum, corpus callosum, internal and external capsule, corona radiata, posterior thalamic radiation, superior and inferior longitudinal fasciculus, fronto-occipital fasciculus, cingulate gyri, fornix, uncinate fasciculus, and tapetum [14].

The UF holds particular significance as a critical neural structure. In the study [15], the focus was on investigating the microstructural pathology of the UF using diffusion tensor imaging in individuals with amnesic MCI, and examining its connection with deficits in memory and emotional processing. The participant pool comprised 16 amnesic MCI patients and 16 healthy controls. Using DTI, FA values of the UF were calculated. Furthermore, the potential relationship with verbal memory and the recognition of emotional facial expressions of the UF was explored. Notably, the FA values of the left UF were lower in the amnesic MCI group, and these values displayed a robust correlation with episodic memory performance among individuals with amnesic MCI. In the realm of emotional recognition, amnesic MCI participants exhibited inferior performance in identifying negative emotions. Strikingly, the FA values of the left UF were correlated with the accuracy of recognizing fearful facial expressions in the amnesic MCI group. In conclusion, the findings underscore the presence of microstructural alterations within the UF among individuals with amnesic MCI. Additionally, these alterations might serve as underlying factors contributing to the observed impairments in memory and emotional processing within the amnesic MCI population.

The study from Fu et al. [16] demonstrated the ODI metric exhibiting significant decreases in the WM of patients with MCI and AD in comparison to healthy controls. The histological interpretation of the reduced ODI pointed towards "reduced orientation dispersion reflects loss of secondary crossing fibers to leave more

aligned neurons in the primary tracts, perhaps mediated by selective axonal degeneration" [17]. Also, the *fiso* was notably found to be elevated in both the MCI and AD groups when compared to the healthy control group [16]. This increase which is especially more pronounced in the AD group than in the MCI group, was primarily observed in the brain stem and bilateral medial temporal lobes, signifying cell shrinkage and decreased tissue volume fraction indicative of atrophy [18].

The models of dMRI offer insights into brain tissue characterization through interpretations. However, as explained earlier, certain metrics have generated conflicting interpretations due to contradictory trends observed, leading to distinct implications. For instance, the *ODI* metric demonstrates an increase in the white matter of individuals with AD in the study by Wen et al. [13], whereas it exhibits a decrease in the study conducted by Fu et al. [16].

Overview of prior investigations regarding the metabolic aspects and tau pathology in the PCC

Herholz et al. conducted a study involving 9 age-matched controls and 25 patients with mild to moderate AD. The primary objective of their investigation was to evaluate metabolic regional and network changes in different AD subtypes, namely Amnesic AD, Multidomain AD, and Visual AD. Their findings revealed a consistent occurrence of significant hypometabolism in PCC across all subtypes. Notably, the visual subtype exhibited distinct occipital hypometabolism. In control subjects, the study identified two prominent clusters of positive regional metabolic correlations. Interestingly, the most significant disruption of the normal correlation pattern was observed in patients with amnesic AD, who paradoxically displayed the least regional focal metabolic deficits. Additionally, the normal positive correlation between the PCC and the hippocampus was absent in all subtypes. In conclusion, the study established that PCC hypometabolism and the breakdown of metabolic correlations between the PCC and the hippocampus constitute the common functional core among all AD subtypes. Notably, network changes surpassed focal regional impairments and were most pronounced in the amnesic subtype [19].

PCC hypometabolism is a recognized key biomarker in Alzheimer's disease (AD). Consequently, the study conducted by [20] aimed to address the question, "Does PCC hypometabolism result from disconnection or local pathology across preclinical and clinical stages of AD?" This investigation encompassed a cohort of 667 subjects, spanning from cognitively normal aging individuals to those with prodromal AD and AD dementia. The volume of the hippocampus and PCC grey matter was determined using volumetric MRI scans, while PCC metabolism was evaluated using FDG PET, and PCC amyloid load was assessed through PET scans. The

study outcomes indicated that in cognitively normal individuals and those in the early stages of mild cognitive impairment (MCI), PCC hypometabolism was solely linked to hippocampal atrophy. However, in late MCI subjects, it was associated with both local and remote atrophy effects, along with local amyloid accumulation. For individuals with AD dementia, PCC hypometabolism was exclusively associated with local atrophy. This implies that the impact of remote pathology on PCC hypometabolism diminishes, while the influence of local pathology increases as AD progresses from preclinical to clinical stages. This pattern is in line with a progressive disconnection of the PCC from downstream cortical and subcortical brain regions.

Jacobs et al. did a study that aims to explore the relationship between tau propagation and structural connectivity, under the influence of increased amyloidosis, and its relevance for memory in a healthy older population [21]. The study design is motivated by a recent animal study investigating tau propagation via connectivity or proximity, showing that tau pathology in hippocampal neurons spreads to connected regions and affects the white matter tracts connecting the hippocampus with the distal region. The study hypothesized that hippocampal volume at baseline would predict abnormal diffusivity of the hippocampal cingulum bundle (HCB) over time, which would in turn be associated with tau accumulation in the downstream-connected posterior cingulate cortex (PCC) and both processes would be associated with memory decline over a 6-year period. The study also investigated the potential moderating role of amyloid in tau propagation and memory decline. They additionally included the uncinate fasciculus (UF) as a control tract, since this tract innervates the medial temporal lobe but not the hippocampus. Furthermore, the UF innervates the prefrontal lobe, a region with limited tau binding in cognitively healthy older individuals. For tau accumulation, they included inferior temporal (IT) tau load as a control measure for spread via proximity versus connectivity. The inferior temporal lobe is spatially proximate to the hippocampus and does not primarily have connections from the HCB.

To motivate their study, they developed a hypothetical model shown on the Figure 1.6. On the figure, the relationships specifically analyzed in the article are within the blue box. The green boxes hypothesize that hippocampal volume loss results from neuronal damage, partially due to early tau pathology in the medial temporal lobe (MTL). As tau PET was acquired later in the study and thus this information was not available at baseline, they could not examine the green boxes. The relationship between hippocampal volume and diffusivity of the HCB was analyzed using both baseline measures of hippocampal volume and change in hippocampal volume over time.

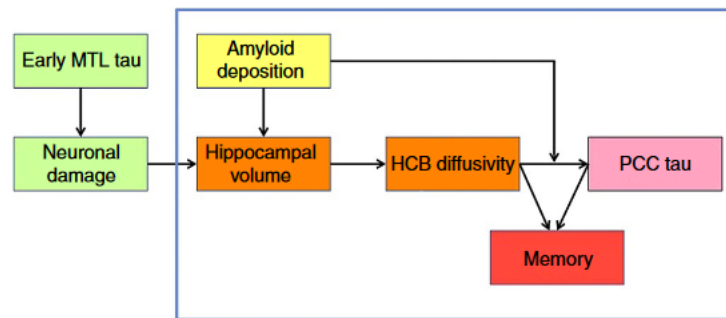


Figure 1.6: The hypothesized model motivating the design and analyses of Jacobs et al.

Over a period of 7 years, a total of 256 participants from the Harvard Aging Brain Study underwent regular imaging and annual neuropsychological assessments. At the beginning of the study, the participants had a median age of 73.5 years (with an interquartile range of 68.5–78.25 years), a median educational level of 16 years (with an interquartile range of 13–18 years), and a median score of 29 points (with an interquartile range of 28–30) on the Mini-Mental State Examination (MMSE) screening test. Of the participants, 145 (60.16%) were female. At baseline, all participants were cognitively healthy based on their MMSE scores, had a Clinical Dementia Rating Scale of 0, and had normal age- and education-adjusted scores on the Logical Memory delayed-recall test. The participants underwent a comprehensive medical and neurological evaluation to ensure that they did not have any significant psychiatric or neurological disorders. The data obtained for the tau pathology and amyloid deposition comes from PET imaging and to measure the microstructural properties, they used DTI.

As a result of their study, Jacobs et al. showed that :

1. Amyloid deposition is associated with increased hippocampal volume loss. Lower hippocampal volume is associated with white matter abnormalities of HCB and UF at baseline.
2. Hippocampal volume predicts change in diffusion over time of HCB, but not in UF.
3. Hippocampal cingulum diffusivity selectively predicts accumulation of tau pathology in the connected PCC in amyloid-positive individuals.
4. Memory-tract diffusivity associations are driven by tau pathology.

Thus, this research indicates that the presence of amyloid leads to the enhanced propagation of tau via the HCB. This confirms that amyloid plays a pivotal role in the sequence of events contributing to the development of tau pathology and resultant memory decline. However, as they did not investigate any possible molecular mechanisms or pathways that may facilitate the spread of tau pathology or how amyloid may strengthen this spread, this remain unanswered questions. Nevertheless, these findings provide a basis for future studies on disease models and suggest that measuring the extent of tau pathology propagation could be a valuable outcome measure for clinical trials focused on early removal of amyloid plaques, as amyloid intensifies the propagation of tau.

1.2.5 Questions of research

From these investigations, a fundamental question has arisen. PCC hypometabolism emerges as the shared functional core across all AD subtypes and can be linked to either local or distant atrophy effects depending on the stage of AD. Furthermore, given that cognitive decline is attributed to PCC hypometabolism : What precisely underlies the hypometabolism in the PCC? This inquiry led to numerous sub-questions : Is it related to tau accumulation within this brain region? Does mean diffusivity in the HCB play a role? Or could it be associated with tau accumulation in the medial temporal lobe? This master thesis aims to comprehensively address all this questions.

Chapter 2

Microstructure analysis

2.1 Methods

2.1.1 Data collection and conversion

Anatomical and diffusion MRI images were acquired at St-Luc University Hospital on a 3T GE (Chicago, IL) *SIGNATM* Premier scanner, equipped with a 48-channel head coil. The anatomical images were obtained with gradient recalled echo MRI sequence with the following properties: repetition time (TR) = 7.192 *ms* and echo time (TE) = 2.912 *ms*. The slice thickness was 1.2*mm* and the voxel size was 1 x 1 x 1 *mm*³. Diffusion MRI images were acquired with a PGSE sequence with the following properties: TR = 4842 *ms* and TE = 77.9 *ms*. A multi-shell diffusion scheme was used with the following acquisition protocol: a baseline with a b-value of 0 [*s/mm*²], a b-value of 1000 [*s/mm*²] (64 directions), a b-value of 2000 [*s/mm*²] (32 directions, with a b-value of 0 after 16 and 32 directions), a b-value of 3000 [*s/mm*²] (32 directions) and a b-value of 5000 [*s/mm*²] (32 directions). The gradient intensities were 30.8, 43.55, 53.34 and 68.86 [*mT/m*] for the shells with b-values of respectively 1000, 2000, 3000 and 5000 [*s/mm*²]. The FOV was 220 x 220 *mm*², the in-plane matrix size was 256 x 256 and the data contained 68 axial slices with 2-mm thickness (no inter-slice gap), leading to a voxel size of 0.8594 x 0.8594 x 2 *mm*³. A multi-slice excitation scheme was used during the acquisition with a hyperband slice factor of 3 to reduce the acquisition time. The duration of the diffusion gradients pulses (δ) was 23.824 *ms* and their onset separation (Δ) was 36.52 *ms*. The DICOM [22] files obtained were converted in Nifti [23] files using the opensource software dcm2niix [24] that has been implanted in the software Bmat created by Colin Vanden Bulcke [25]. In total, the data of 65 patients spanning from MCI to AD dementia were retrieved.

Tau accumulation data and metabolism data were obtained using PET scan

imaging by Vincent Maloteaux. Other data about the patients like the age, gender, education score, MMSE score, cognition score, amyloid deposition and the presence or not of the allele APOE4 were provided also by Vincent Maloteaux in the format of csv or excel files. Unfortunately, the dataset only encompassed data from 45 out of the total 65 patients. Consequently, the analysis was performed on all 65 patients when feasible, and for the remaining instances, it was carried out on the available 45 patients.

2.1.2 Image processing

Nifti files of raw data were preprocess on the cluster of the UCLouvain Manceback using Elikopy. Elikopy [26] is a Python library simplifying the processing of diffusion imaging for microstructural analysis. It uses Python packages such as DiPy [27], Dmipy [28] and MF [8] to enhances existing pipeline frameworks by incorporating a comprehensive quality assessment and quality report for each processed subject, ensuring standardization and reproducibility, minimizing error propagation, and increasing sensitivity. Moreover, it enables clinicians to perform rapid preprocessing for various studies with minimal expertise.

The software proposes a preprocessing following several steps shown on Figure 2.1 [29]:

1. **Reslice :** In cases where raw data is not in its original resolution, reslicing may be necessary. Typically, MRI scanners apply automatic interpolation to enhance the resolution of the data for clinical purposes. However, this interpolation does not actually increase the intrinsic resolution. While this can be useful for clinicians, it is often undesirable for research purposes as it increases computation time and introduces uncorrelated noise that can negatively impact the performance of MPPCA denoising algorithms. Additionally, interpolation can cause issues when performing Gibbs ringing correction. Reslicing offers a solution to mitigate the effects of mandatory interpolation during acquisition. In this work reslicing is required as the raw data has been interpolated. The raw data were of dimension 256x256x68 and are after reslicing of dimension 110x110x68.
2. **Brain extraction :** To enhance the efficiency of subsequent steps and enable the use of other image processing algorithms, the brain is extracted from surrounding tissues, including the skull. This preprocessing step is necessary. At the end of the preprocessing, a final brain mask is provided as output, which has been adjusted to account for all the applied preprocessing steps.

3. **MPPCA Denoising** : To reduce the Rician noise that is found in MR images, Elikopy chose to use the Marchenko-Pastur Principal Component Analysis method as it is fast and it does not blur the image.
4. **Gibbs ringing correction** : Typically, diffusion-based estimates in diffusion-weighted imaging are impacted by Gibbs oscillations. To address this issue, DiPy utilizes the `GIBBS_REMOVAL` function. However if the data does not suffer from this, it is not advised to use this correction as it will blur microstructural features. It is not used in this work as the data was not affected by Gibbs oscillations.
5. **Susceptibility field estimation** : Differences in magnetic susceptibility near junctions of tissues can create susceptibility distortions. Those distortions are estimated using Topup from FSL. It requires multiple phase encoding directions but when there is only one available, it uses instead a generated synthetic volume based on a T1 image using Synb0-DisCo. This was the case for the data used in this work. The susceptibility distortions estimated in this step can then be corrected in the next one.
6. **Eddy and motion correction** : It corrects the susceptibility distortions estimated during last step, but also motions and Eddy current induced distortions. Probably due to a lot of noise, the data of this work did not use this step as it was taking too much time of computation. Therefore it will be a factor during the study as the corrections have not been made for these data.
7. **Bias Field Correction** : This is the last step of the preprocessing and its purpose is to correct signal variability in tissues of the same type, which can affect the calculation of microstructural metrics. However this step is not used in this work.

This preprocessing step has not been completed due to a problem with the Eddy and motion correction, therefore only the reslice and the MPPCA Denoising has been applied. This should not be a problem as the patients did not move that much as it can be seen on Figure 2.2 but it must be taken into account when interpreting results.

When the preprocessing is done, a white matter mask is applied to extract specific region of interest and to speed up computation of the microstructural features. The Elikopy pipeline allows to compute these features from DTI and multi-compartment models such as DIAMOND, NODDI and MF. This is what has been used in this work to analyse the microstructure of the brain of patients.

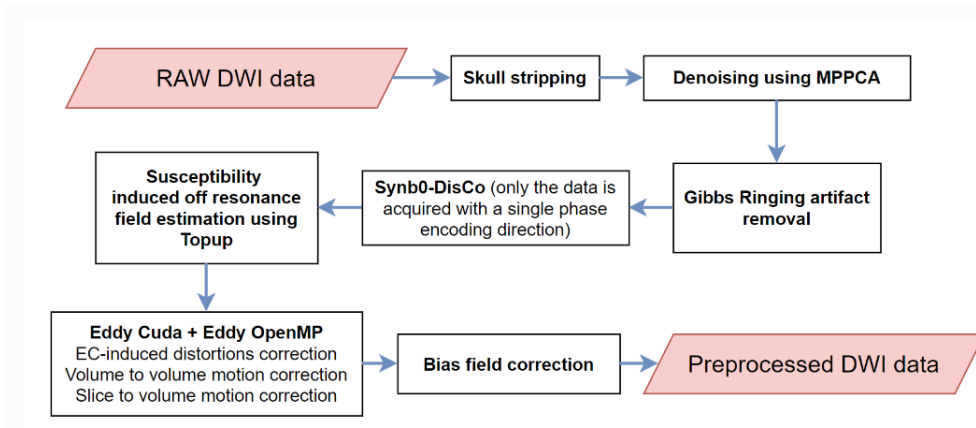


Figure 2.1: Preprocessing steps.

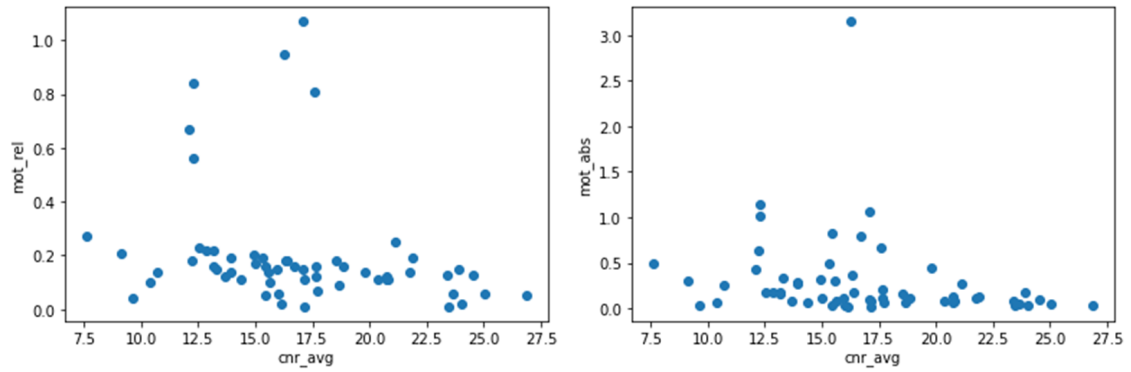


Figure 2.2: Scatter plot representing the relative motion and absolute motion compared to the noise for each patient.

2.1.3 Regions of Interest

In order to address the research questions, various regions of interest were identified. Specifically, following the approach outlined in the study by Jacobs et al. [21], the researchers selected the HCB and PCC regions. So this study went with a more detailed focus on the posterior cingulate cortex, the isthmus cingulate cortex, the entorhinal cortex, and the parahippocampal cortex, which are depicted in Figure 2.3. Additionally, the hippocampus and amygdala regions were chosen and are also represented in Figure 2.4. To assess connectivity between these regions, the cingulum was included in the analysis and is depicted in Figure 2.5. The fasciculus uncinata was also chosen as a control region, and its location is displayed in Figure 2.5.

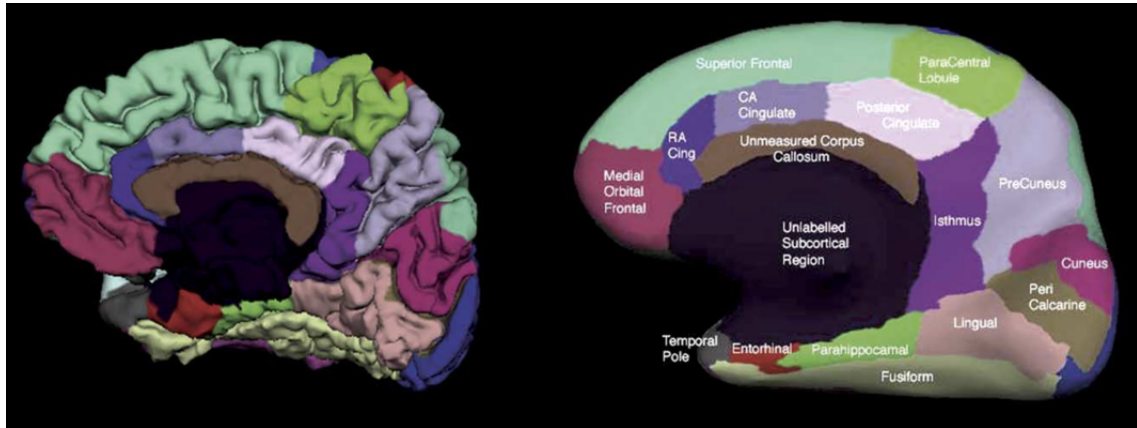


Figure 2.3: Representation of the posterior cingulate cortex, the isthmus, the parahippocampal cortex and the entorhinal cortex.

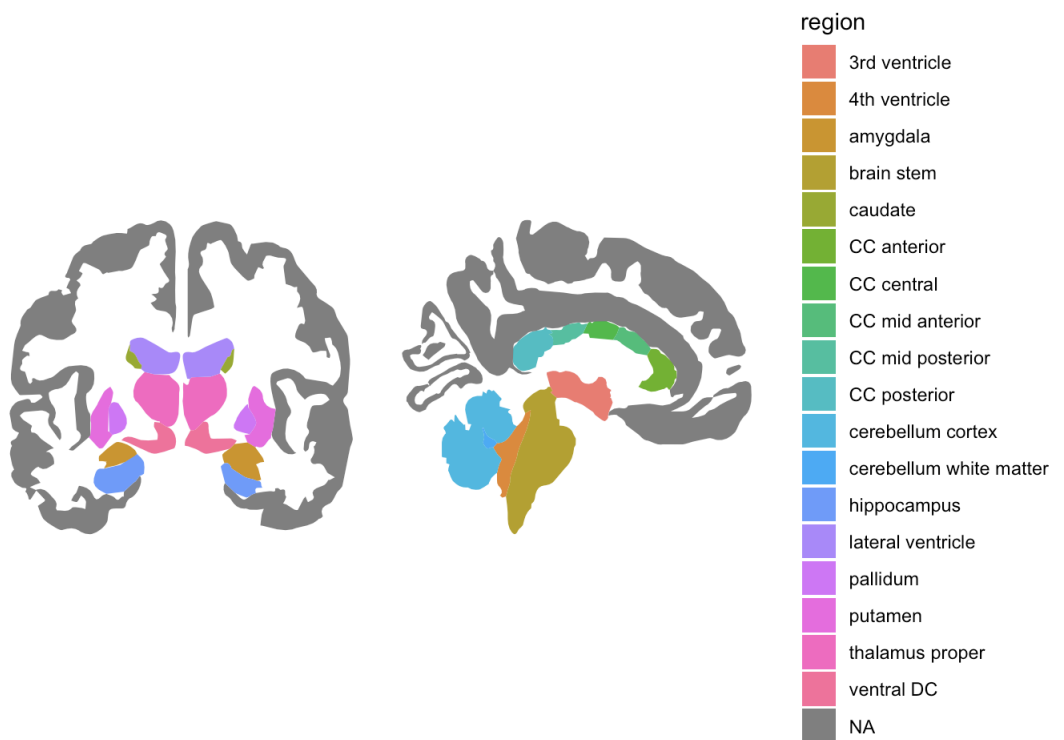


Figure 2.4: Representation of the amygdala and the hippocampus.

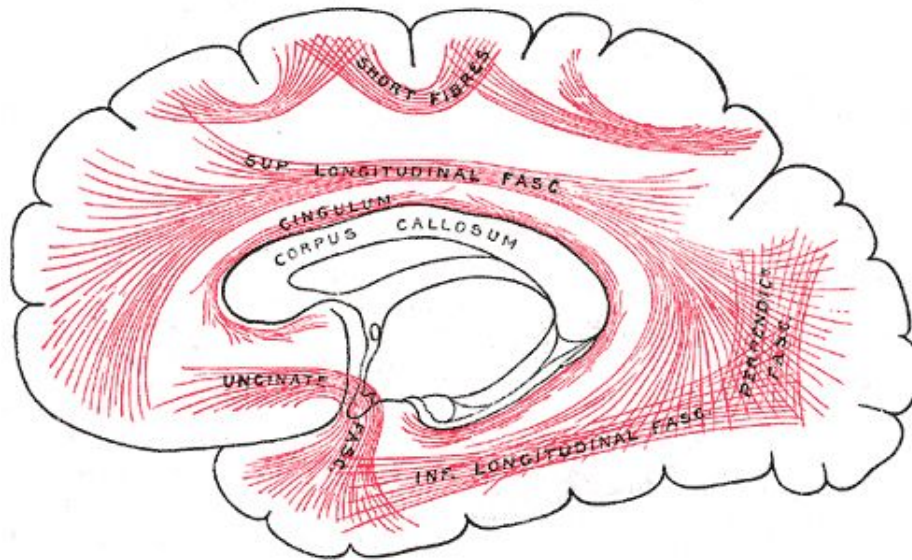


Figure 2.5: Representation of the uncinate fasciculus and the cingulum.

Atlas collection

The region of interest come from atlases. The cortex regions come from the Aparc atlas and the amygdala and the hippocampus for the Aseg atlas composing the Desikan-Killiany atlas [30],[31]. The Desikan-Killiany cortical atlas is categorized as a gyral-based atlas, it defines a gyrus as extending between the bottoms of two neighboring sulci. In other words, a gyrus encompasses both the visible portion on the pial view and the surrounding banks of the sulci that define it.

The cingulum bundle comes from a probabilistic atlas from NatBrainLab [32] based on a method developed by Catani et al. [33] to reconstruct white matter pathways using a region of interest (ROI) approach. For its part, the fascicle uncinate comes from the XTRACT HCP Probabilistic Tract Atlases. In the study conducted by Warrington et al. published in NeuroImage [34], a total of 42 probabilistic tract atlases were created using data from 1021 subjects participating in the Human Connectome Project. The atlases were generated by applying XTRACT to each subject's minimally preprocessed diffusion MRI data, following the methods described in Glasser et al. and Sotiropoulos et al. [35]. The resulting tract estimates were converted into binary form using a threshold and then averaged across the entire cohort. This process produced population percent overlap maps for the major white matter fiber bundles.

Cingulum division

To address the research questions effectively, the cingulum bundle has been divided into multiple regions, as not all parts of it are relevant. The purpose behind this division is to explore different hypotheses by selectively including or excluding specific regions connected by this tract.

The first division focuses on the segment of the cingulum passing through the entorhinal cortex, the hippocampus and goes to the center of the isthmus cingulate cortex. Another division, of particular interest to us, encompasses the entorhinal cortex, the hippocampus, and the entire isthmus cingulate cortex. Lastly, a third division includes the entorhinal cortex, the hippocampus, the isthmus cingulate cortex, and the posterior cingulate cortex. By dividing the cingulum bundle in this manner, we can examine the different regions and assess their individual contributions to the research questions at hand. The visual representation on Figure 2.6 highlights the distinct divisions of the cingulum.

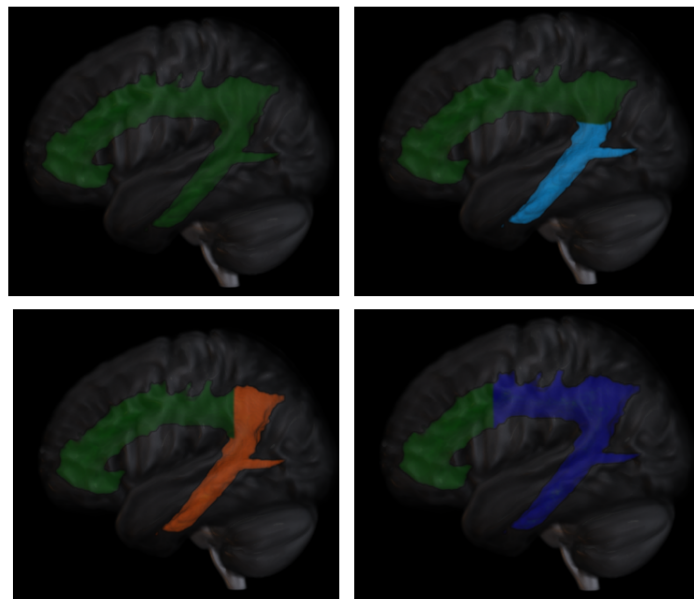


Figure 2.6: Representation of the division of the cingulum. The cingulum bundle is shown in green. In the top right corner, the first division is illustrated in light blue. Moving to the bottom left, the second division is depicted in orange. Finally, in the bottom right, the last division is shown in dark blue.

Atlas registration

After acquiring these atlas, they undergone registration. First the Desikan-Killiany atlas has been registered to the Montreal Neurological Institute 152 (MNI152) space, then atlases were created using labels for the ROI. The XTRACT and NatBrainLab atlases, on their side, were already in the space of the FA map from HCP1065 standard-space.

Since every subject included in this master's thesis has a distinct brain structure, the maps within the atlases needed to undergo registration specific to each individual. This registration process was essential to accurately delineate the relevant brain areas for the analysis conducted in this study.

Therefore registration of each patient has been done with the specific FA map from HCP1065 standard-space for the XTRACT and using the FA map of each patient calculated by the DTI model in `eliko`. For the Desikan-Killiany atlases, the MNI152 T1 image has been used with the first volume of the orientation distribution function of the white matter that has been calculated with `eliko` using the multi-shell multi-tissue constrained spherical deconvolution (MSMT-CSD_WM_ODF). Finally, for the NatBrainLab atlases, a T1 image of average brain provided by NatBrainLab has been used. The maps used are shown on the Figure 2.7.

The registration process was conducted using the Python module `Dipy`, utilizing a tutorial provided within the `Dipy` documentation as the basis for implementation. The Figure 2.8 shows the result from this registration on the patient 9 for the three specific atlases. The first column of the first and third bloc represent the MSMT-CSD_WM_ODF map, the first column of the second bloc represent the FA map, the second column of each bloc represent the stacked maps of the first and third column while finally the last column of each bloc represent respectively the T1 averaged map from NatBrainLab, the FA map in HCP1065 standard-space and the MNI152 T1 image.

The mapping is then applied for the region of interest to get them in the patient space. It allows to analyse the right region in each patient and to continue with the microstructure analysis.

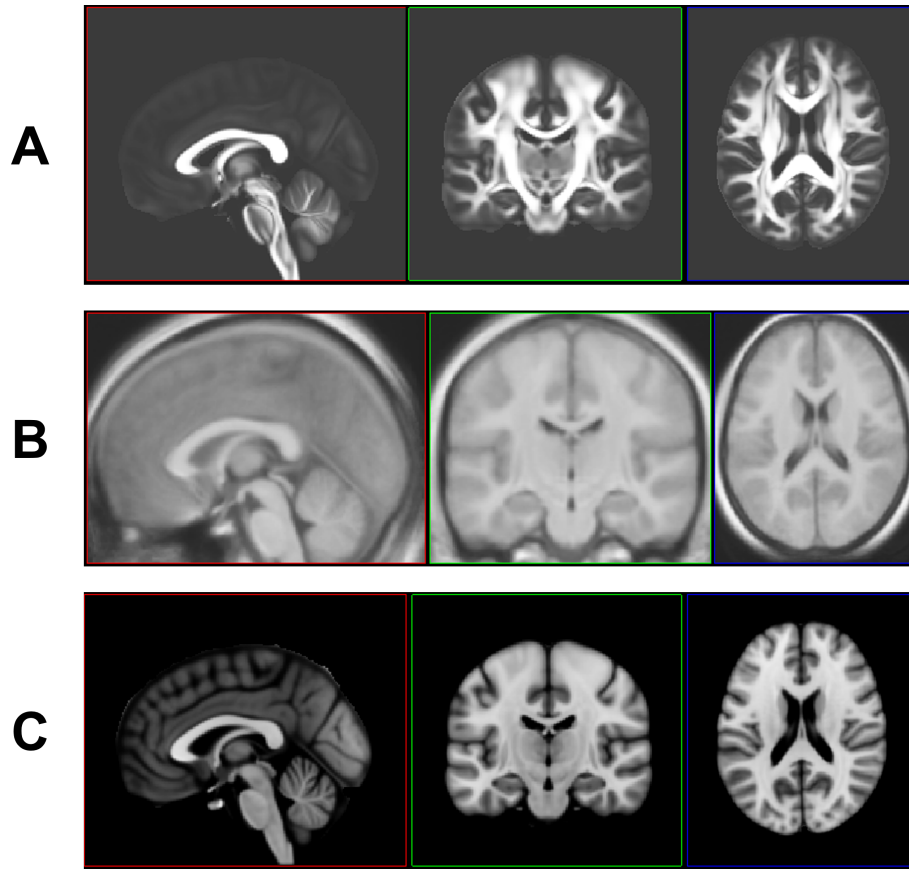


Figure 2.7: **A** : FA map from HCP1065 standard space. **B** : T1 image of average brain from NatbrainLab. **C** : MNI152 T1 image.

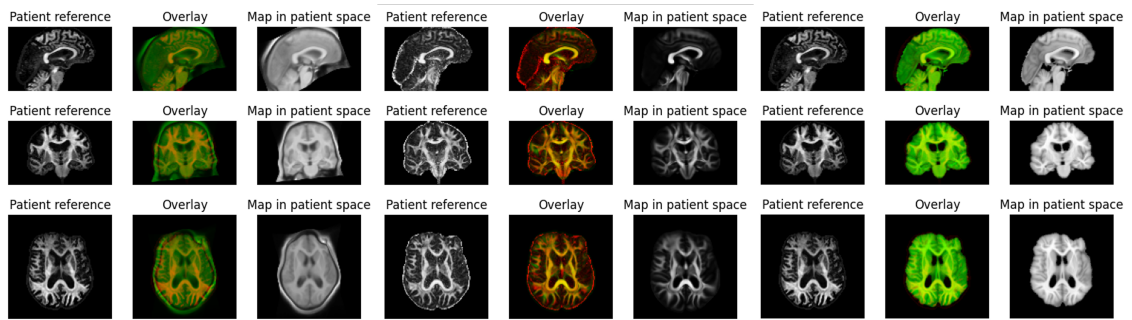


Figure 2.8: Representation of the FA and the first volume of MSMT-CSD_WM_ODF with the registration of the three atlases. On the left there is the T1 averaged brain from NatBrainLab, in the middle the FA map from HCP1065 standard-space and finally on the right the MNI152 T1 image.

2.1.4 Microstructure analysis

The aim of the microstructure analysis is to summarize the variations of each metrics of each models in the ROI selected. Therefore they were computed using ElikoPy incorporating Dipy for the DTI metrics [27], a research code developed by B. Scherrer to assess DIAMOND metrics [7], Dmipy package for Noddi [28] and for the MF metrics it incorporates a Python library created by G. Rensonnet, who is the primary author of the MF methodology [8].

DTI analysis

The DTI model has been used to compute the fractional anisotropy, the axial diffusion, the radial diffusion and the mean diffusion (FA, AxD, RD, MD). The meanings of these metrics are explained in the section 1.1.2. These metrics are displayed on the Figure 2.9.

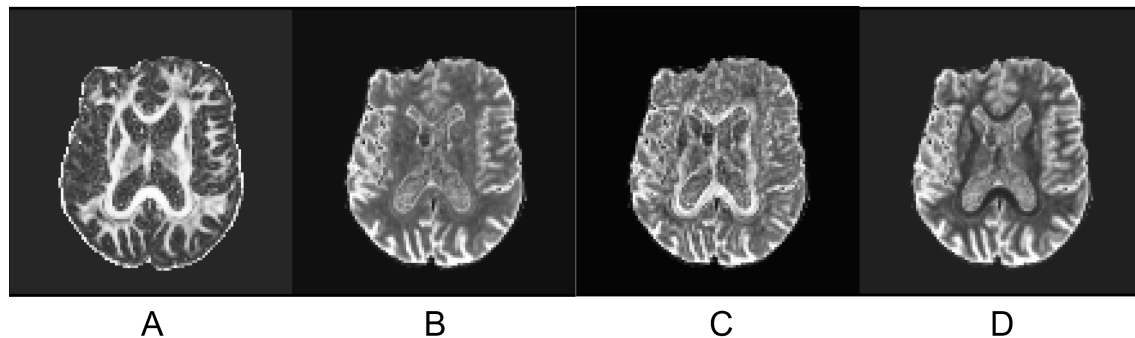


Figure 2.9: Representation of **A** : FA, **B** : MD, **C** : AxD, **D** : RD.

DIAMOND analysis

The DIAMOND model can provide various metrics through the ElikoPy pipeline. Initially, fractions files were retrieved, consisting of two files representing the first fiber population and the second fiber population as ElikoPy estimates by default a maximum of two fascicules per voxel. These files were named `frac_f0` and `frac_f1`.

Additionally, files named `t0` and `t1` were examined, which represent tensors from the first and second fiber populations. Each tensor contains six components, allowing the construction of the D tensor as described in section 1.1.4. This tensor also facilitates the computation of four DTI metrics (`cFA`, `cMD`, `cAxD`, `cRD`). Each tensor yielded two maps per metric, one for each fiber population. This

incorporation of fractions as weights on different compartments was necessary for this purpose. Consequently, the newly computed metrics were denoted as **wFA**, **wMD**, **wAxD**, and **wRD**, with the 'w' signifying weighted. They were calculated using the following formulas :

$$wFA = \frac{frac_{f0} * cFA(f0) + frac_{f1} * cFA(f1)}{frac_{f0} + frac_{f1}}. \quad (2.1)$$

Using the same equation we can compute **wMD**, **wAxD** and **wRD**. These metrics help overcome the primary limitations of DTI by addressing fiber crossing within a voxel, a capability that DTI lacks. These metrics are shown on the Figure 2.10.

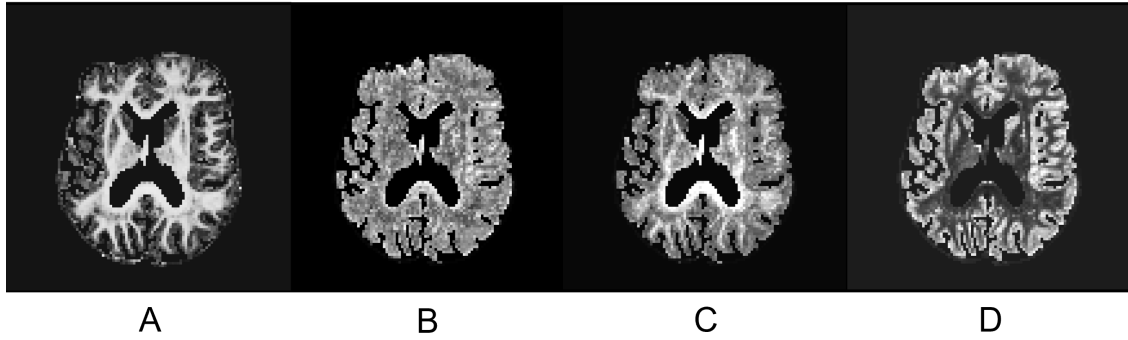


Figure 2.10: Representation of **A** : **wFA**, **B** : **wMD**, **C** : **wAxD**, **D** : **wRD**.

NODDI analysis

Elikopy outputs several metrics from this models, only four of them are retained. We have the free water volume fraction (**fiso**), the intracellular volume fraction (**fintra**), the extracellular volume fraction (**fextra**) and the orientation dispersion index (**ODI**). These metrics have been explained in the section 1.1.3 and are shown on the Figure 2.11.

On the left, high **fiso** values are observed in the ventricles, which correspond to the presence of cerebrospinal fluid. In contrast, the values are relatively low in the rest of the brain. On the middle left side of the Figure, the quantification of intracellular matter reveals low values in the ventricles where no fibers are expected, while high values are observed in white matter. Similarly, on the middle right, the importance of the extracellular compartment is highlighted in a similar map, but with higher values surrounding WM tracts, confirming its biological significance. Finally, the orientation dispersion index map exhibits very high values in the CSF, where no directionality is observed, and low values throughout the brain where WM tracts are present.

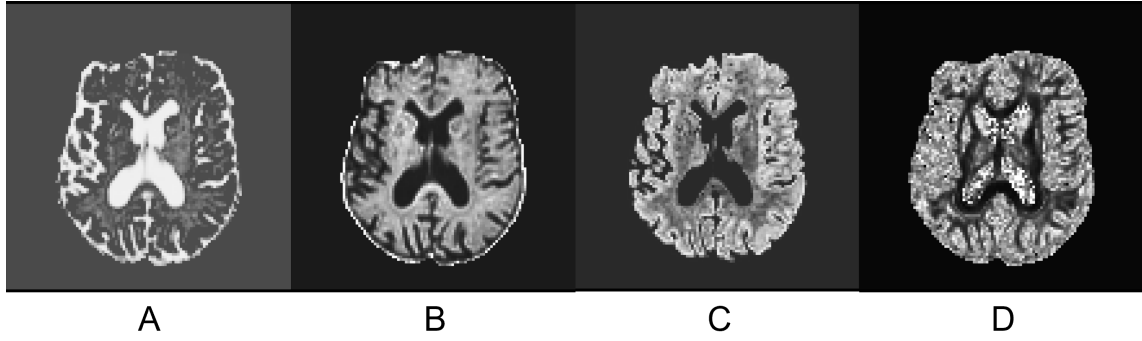


Figure 2.11: Representation of **A** : fiso, **B** : fintra, **C** : fextra, **D** : ODI.

Microstructure Fingerprinting analysis

Microstructure fingerprinting has several metrics as output. However, similar to the DIAMOND model, the MF method allows for the identification of different fiber populations within a voxel. Therefore, the metric known as the fiber volume fraction (**fvf**) received in output, separately for each fiber population followed the same equation as mentioned earlier. A weighted **fvf** (**wfvf**) was then introduced as a common metric. The **wfvf** represents the proportion of fibers from both populations within the voxel, excluding the CSF compartment. It was calculated using the following formula:

$$wfvf = \frac{frac_f0 * fvf_f0 + frac_f1 * fvf_f1}{frac_f0 + frac_f1} = \frac{fvf_tot}{frac_ftot} \quad (2.2)$$

The difference between **fvf_tot** and **wfvf** is that **fvf_tot** estimates the proportion of fibers in the entire voxel whereas **wfvf** only considers the fiber compartment and evaluates the concentration of the fibers. These two metrics are shown on the Figure 2.12

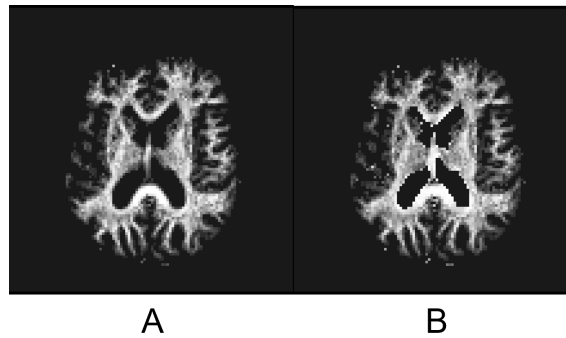


Figure 2.12: Representation of **A** : fvf_tot, **B** : wfvf.

2.1.5 Tractography

Tractography serves as a 3D modeling technique for visually representing nerve tracts, utilizing data acquired through diffusion MRI [36]. Within this master's thesis, it is employed to illustrate the studied fascicle of the cingulum and to ascertain the quantity of fibers it encompasses. Consequently, employing the Python module `dipy`, a tractogram of the cingulum bundle is generated. To exclusively encompass the fibers traversing the cingulum bundle, a target method is used. This approach enables the retention of fibers passing through the selected ROI, namely the posterior cingulate cortex, the second division of the cingulum, and the entorhinal regions for both the left and right hemispheres. Subsequently, the fiber count within this tractogram is computed, serving as a novel variable for subsequent statistical analysis. Other ROIs were tested but the tractograms resulting were containing fibers outside of the scope of the cingulum bundle. Visualisation of these tractograms are done using the software TrackVis [37].

2.1.6 Statistical analysis

Subsequent to data collection, a comprehensive statistical analysis encompassing various variables and metrics was executed. Initially, the mean values and variances for each metric were calculated within each ROI. As some ROIs were probabilistic atlases, a threshold of 30% has been arbitrarily set to avoid taking metrics from regions adjacent to the ROIs. This procedure led to the creation of a dataset containing these computed values. In this dataset, columns represent the means and variances of metrics for distinct ROIs, while rows pertain to individual patients.

Incorporated into this dataset were additional parameters such as age, gender, MMSE score, PET tau values, PET fdg values, educational attainment, FCSRT cognition score, presence of the APOE4 allele, and amyloid- β deposition. The dataset initially encompassed informations from 65 patients; however, this number decreases to 45 patients when this additional data were incorporated due to the unavailability of these data for all patients. Correlation and linear regression techniques were subsequently employed to investigate relationships between different variables. The initial step involved conducting simple linear regressions between isthmus cingulate metabolism and metrics from various ROIs, encompassing both right and left hemispheres. This involved separate linear regressions for each metric across the three cingulum divisions and the control region, the uncinate fasciculus.

Following this, the entorhinal metabolism was integrated into the statistical model, followed by the inclusion of additional variables to comprehensively assess their individual impacts. The resulting outcomes are presented in the form of a

table, visualized in Figure 2.13, showcasing the significance of each variable and the overall regression. The computations for these regressions were executed utilizing the statsmodels Python module [38].

Numerous correlation maps were also generated, encompassing various relationships. These included correlations between the accumulation of tau in the entorhinal cortex and the metabolism of the isthmus cingulate, correlations between tau accumulation and isthmus cingulate metabolism, correlations between entorhinal cortex metabolism and isthmus cingulate metabolism, and lastly, correlations between tau accumulation in the entorhinal cortex and tau accumulation in the isthmus cingulate. Additional correlation maps and linear regression analyses were conducted involving various metrics and the FCSRT cognition score.

Furthermore, regression analyses were conducted, focusing on the connection between isthmus cingulate cortex metabolism and the number of fibers present in the tractogram of the cingulum bundle.

OLS Regression Results						
Dep. Variable:	ctx_rh_isthmuscingulate_fdg_nopvc		R-squared:	0.281		
Model:	OLS		Adj. R-squared:	0.189		
Method:	Least Squares		F-statistic:	3.046		
Date:	Thu, 04 May 2023		Prob (F-statistic):	0.0205		
Time:	03:07:08		Log-Likelihood:	23.554		
No. Observations:	45		AIC:	-35.11		
Df Residuals:	39		BIC:	-24.27		
Df Model:	5					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
const	1.6654	0.605	2.751	0.009	0.441	2.890
mean_AD_Cingulum_EHI_right	-752.0817	512.660	-1.467	0.150	-1789.035	284.871
Age	-0.0020	0.004	-0.545	0.589	-0.009	0.005
Sex	-0.0476	0.055	-0.861	0.395	-0.159	0.064
Education	-0.0384	0.037	-1.039	0.305	-0.113	0.036
ctx_rh_entorhinal_fdg_nopvc	0.6108	0.231	2.640	0.012	0.143	1.079
Omnibus:	2.826	Durbin-Watson:	2.375			
Prob(Omnibus):	0.243	Jarque-Bera (JB):	1.978			
Skew:	-0.499	Prob(JB):	0.372			
Kurtosis:	3.244	Cond. No.	1.62e+06			
Notes:						
[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.						
[2] The condition number is large, 1.62e+06. This might indicate that there are strong multicollinearity or other numerical problems.						

Figure 2.13: Example of a results table.

2.2 Results

After applying the methodology, a substantial number of outcomes were derived for each microstructural model. These outcomes are presented in their respective dedicated subsections and will subsequently be subject to comprehensive discussion. However, given the primary objective of evaluating the metabolism of the posterior cingulate, initial linear regression analyses were conducted. These analyses involved examining the relationship between entorhinal metabolism and isthmus cingulate metabolism, along with a regression comparing the accumulation of tau in the entorhinal region and in the isthmus cingulate. The resulting figures, labeled as Figure 2.14 and Figure 2.15, were produced to visually represent these regression analyses.

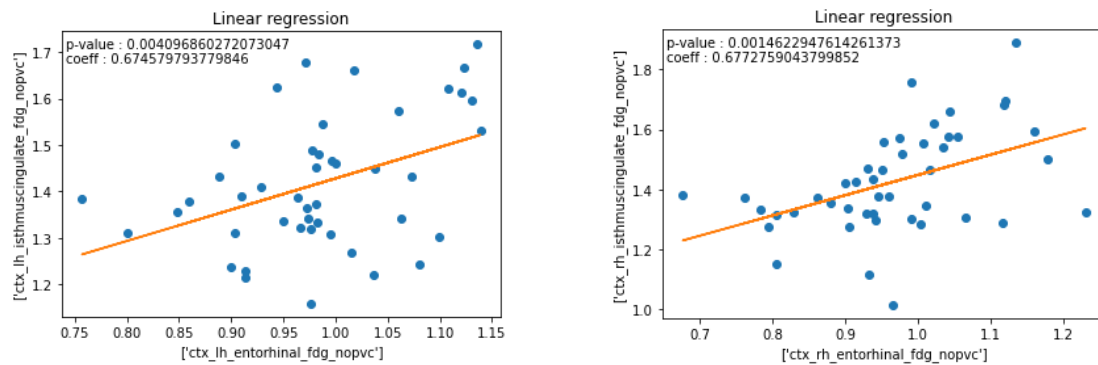


Figure 2.14: Linear regressions between the metabolism of the entorhinal cortex and the isthmus cingulate cortex.

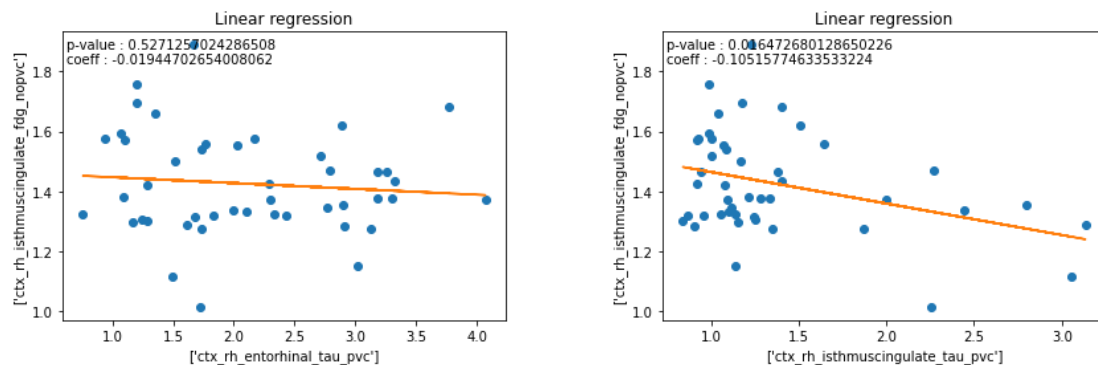


Figure 2.15: Linear regression between the tau accumulation of the entorhinal cortex and the isthmus cingulate cortex. Second linear regression is about the tau accumulation in the isthmus cingulate and his metabolism.

Initial observations suggest a noteworthy correlation between the metabolic activities of the two regions, which holds potential for illuminating subsequent findings. Nevertheless, it appears that a substantial relationship doesn't exist between the accumulation of tau in the entorhinal cortex and in the isthmus cingulate cortex. However, a significant connection is evident between tau pathology in the isthmus cingulate and its metabolic activity. Despite these findings, correlation maps generated using the seaborn Python module [39] demonstrated no noteworthy correlations between metabolic activity and tau pathology in both the entorhinal and isthmus cingulate cortices.

An additional regression analysis was conducted to explore the link between the isthmus cingulate metabolism and the results from the FCSRT cognition tests. The data from two specific tests, namely FCSRT Free Recall and FCSRT Total Recall, were collected and subjected to simple linear regression. Consequently, the analysis highlighted that only FCSRT Free Recall exhibited significance in predicting the metabolic activity of the isthmus cingulate cortex in the left hemisphere. This significant relationship is depicted in Figure 2.16, whereas other associations did not attain statistical significance.

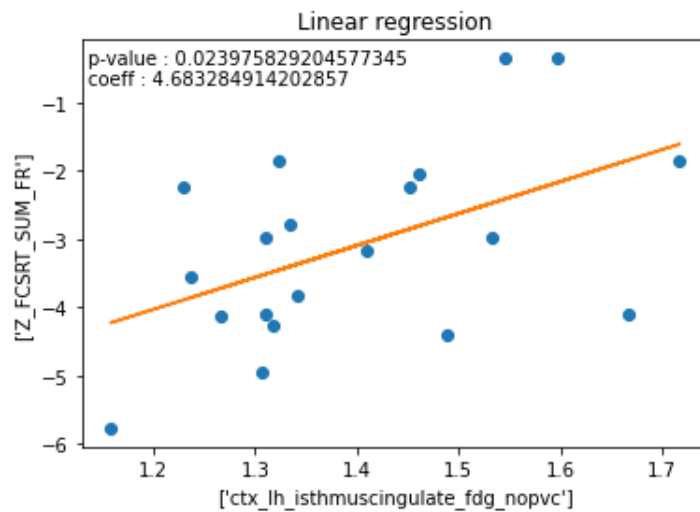


Figure 2.16: Linear regression between the metabolism of the isthmus cingulate cortex in the left hemisphere and the result from the FCSRT FR cognition test.

2.2.1 DTI analysis

Four metrics are derived from DTI: fractional anisotropy, axial diffusivity, radial diffusivity, and mean diffusivity. Initially, simple regression analyses were performed, assessing the connection between isthmus cingulate metabolism and the aforementioned metrics within the first, second, and third divisions of the cingulum bundle, as well as with the uncinate fasciculus. The results of these regressions' p-values are visually depicted in Figure 2.17. In this representation, the minimal value below 0.05 are highlighted in green, indicating statistical significance, while the maximal value that are not significant are shown in red. Yellow represents values between. Additionally, the direction of the linear regression line is indicated by an arrow, with a green upward arrow suggesting positive correlation, and a red downward arrow indicating the inverse relationship. This table serves the purpose of summarizing the obtained results and will aid in the analysis of other metrics.

DTI Regression results						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	AxD cingulum first division	0,720199	↓	0,2451479	↓
Simple	fdg isthmus cingulate	FA cingulum first division	0,156	↑	0,016	↑
Simple	fdg isthmus cingulate	MD cingulum first division	0,453577	↓	0,0335881	↓
Simple	fdg isthmus cingulate	RD cingulum first division	0,30742	↓	0,008315	↓
Simple	fdg isthmus cingulate	AxD cingulum second division	0,34779	↓	0,0729	↓
Simple	fdg isthmus cingulate	FA cingulum second division	0,04558	↑	0,0045	↑
Simple	fdg isthmus cingulate	MD cingulum second division	0,134489	↓	0,00456	↓
Simple	fdg isthmus cingulate	RD cingulum second division	0,0755	↓	0,001286	↓
Simple	fdg isthmus cingulate	AxD cingulum third division	0,21203	↓	0,124964	↓
Simple	fdg isthmus cingulate	FA cingulum third division	0,022064	↑	0,008842	↑
Simple	fdg isthmus cingulate	MD cingulum third division	0,0575	↓	0,010654	↓
Simple	fdg isthmus cingulate	RD cingulum third division	0,03308	↓	0,006009	↓
Simple	fdg isthmus cingulate	AxD uncinate fasciculus	0,473532	↑	0,7501	↑
Simple	fdg isthmus cingulate	FA uncinate fasciculus	0,04418	↑	0,8734	↓
Simple	fdg isthmus cingulate	MD uncinate fasciculus	0,962725	↓	0,52384677	↓
Simple	fdg isthmus cingulate	RD uncinate fasciculus	0,485157	↓	0,1678	↓

Figure 2.17: Results table of simple linear regressions between DTI metrics and the metabolism of the isthmus cingulate cortex.

A noteworthy observation is the relatively higher significance of the metrics for the right hemisphere compared to the left. Overall, the metrics exhibit significance, except in the case of the control region. To delve further, the entorhinal metabolism was included as a covariate, leading to the execution of multiple linear regression. The results are presented in Figure 2.18, demonstrating general significance for the model. However, a closer examination of each independent variable's contribution reveals the consistent significance of the relationship between entorhinal cortex metabolism and isthmus cingulate cortex metabolism, aligning with the earlier findings in Figure 2.14. Similar to previous observations, the DTI metrics exhibit the same trend, with axial diffusivity (AxD) exhibiting lower significance compared to radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA). Notably, the uncinate fasciculus metrics remain relatively insignificant. The robust results from the DTI model warrant in-depth discussion in the dedicated section.

DTI Regression results									
Left Hemisphere					Right Hemisphere				
Metrics	Global P-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics	Global P-value	fdg p-value	Metrics p-value	Tendency fdg
AxD 1	0,017	0,005	0,953	↓	↓	0,00465	0,002	0,393	↓
FA 1	0,00629	0,005	0,16	↑	↑	0,000875	0,004	0,045	↑
MD 1	0,0153	0,005	0,638	↓	↓	0,00156	0,004	0,089	↓
RD 1	0,0123	0,006	0,422	↓	↓	0,000604	0,005	0,029	↓
AxD 2	0,0134	0,006	0,49	↓	↓	0,00251	0,003	0,163	↓
FA 2	0,00257	0,005	0,053	↑	↑	0,000433	0,006	0,02	↑
MD 2	0,0075	0,006	0,203	↓	↓	0,000448	0,007	0,021	↓
RD 2	0,00462	0,006	0,108	↓	↓	0,000181	0,009	0,007	↓
AxD 3	0,0111	0,007	0,357	↓	↓	0,00425	0,004	0,341	↓
FA 3	0,0018	0,007	0,035	↑	↑	0,000588	0,005	0,028	↑
MD 3	0,0047	0,008	0,11	↓	↓	0,000996	0,007	0,052	↓
RD 3	0,00281	0,007	0,059	↓	↓	0,000559	0,006	0,027	↓
AxD control	0,00791	0,003	0,218	↓	↓	0,00415	0,001	0,329	↓
FA control	0,00513	0,011	0,123	↑	↑	0,00124	0,007	0,067	↑
MD control	0,0148	0,004	0,595	↓	↓	0,00667	0,002	0,899	↓
RD control	0,017	0,006	0,911	↓	↓	0,00557	0,004	0,541	↓

Figure 2.18: Results table of multiple linear regressions between DTI metrics, the metabolism of the entorhinal cortex and the isthmus cingulate cortex.

As amyloid- β plays a pivotal role in understanding AD pathology, a separate linear regression was conducted with DTI metrics and isthmus cingulate cortex metabolism, focusing exclusively on patients exhibiting either amyloid pathology or a lack thereof. The outcomes of this regression are visualized in Figure 2.19. Comparing these results with those in Figure 2.17, it is evident that, while generally less significant, the DTI metrics retain more significance in the amyloid-positive population. This implies the potential impact of amyloid status on these results.

DTI Regression results with amyloid positif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	AxD cingulum second division	0,2833	↓	0,1032	↓
Simple	fdg isthmus cingulate	FA cingulum second division	0,098986	↑	0,047138	↑
Simple	fdg isthmus cingulate	MD cingulum second division	0,1321	↓	0,0132	↓
Simple	fdg isthmus cingulate	RD cingulum second division	0,107	↓	0,008676	↓
DTI Regression results with amyloid negatif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	AxD cingulum second division	0,99881	↑	0,57837	↓
Simple	fdg isthmus cingulate	FA cingulum second division	0,3347	↑	0,05569	↑
Simple	fdg isthmus cingulate	MD cingulum second division	0,74369	↓	0,212364	↓
Simple	fdg isthmus cingulate	RD cingulum second division	0,55319	↓	0,1	↓

Figure 2.19: Results table of simple linear regressions between DTI metrics and the metabolism of the isthmus cingulate cortex with amyloid population.

Figure 2.20 indicates a regression p-value of 0.0106, with the FA p-value at 0.003, while the contribution of entorhinal cortex tau pathology registers a p-value of 0.294. This suggests that, even with the contribution of a significant metric like FA from the DTI model, the accumulation of tau in the entorhinal cortex remains less significant, consistent with the findings in Figure 2.15. Conversely, Figure 2.21 reaffirms that tau accumulation in the isthmus cingulate remains a crucial predictor of isthmus cingulate metabolism, as previously identified in Figure 2.15, even when accounting for DTI metrics.

Dep. Variable:	ctx_rh_isthmuscingulate_fdg_nopvc	R-squared:	0.195			
Model:	OLS	Adj. R-squared:	0.156			
Method:	Least Squares	F-statistic:	5.071			
Date:	Wed, 03 May 2023	Prob (F-statistic):	0.0106			
Time:	23:43:29	Log-Likelihood:	21.004			
No. Observations:	45	AIC:	-36.01			
Df Residuals:	42	BIC:	-30.59			
Df Model:	2					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
const	0.4397	0.337	1.306	0.199	-0.239	1.119
mean_FA_Cingulum_EHI_right	2.2479	0.723	3.107	0.003	0.788	3.708
ctx_rh_entorhinal_tau_pvc	-0.0298	0.028	-1.064	0.294	-0.086	0.027
Omnibus:	1.597	Durbin-Watson:	2.525			
Prob(Omnibus):	0.450	Jarque-Bera (JB):	0.751			
Skew:	0.073	Prob(JB):	0.687			
Kurtosis:	3.616	Cond. No.	85.2			

Figure 2.20: Results of a multiple linear regression between FA, tau accumulation in the entorhinal cortex and the metabolism of the isthmus cingulate cortex.

Dep. Variable:	ctx_rh_isthmuscingulate_fdg_nopvc	R-squared:	0.304			
Model:	OLS	Adj. R-squared:	0.269			
Method:	Least Squares	F-statistic:	8.720			
Date:	Wed, 16 Aug 2023	Prob (F-statistic):	0.000719			
Time:	18:20:42	Log-Likelihood:	22.909			
No. Observations:	43	AIC:	-39.82			
Df Residuals:	40	BIC:	-34.53			
Df Model:	2					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
const	0.5923	0.324	1.830	0.075	-0.062	1.246
ctx_rh_isthmuscingulate_tau_pvc	-0.1119	0.039	-2.905	0.006	-0.190	-0.034
mean_FA_Cingulum_EHI_right	2.1137	0.686	3.082	0.004	0.728	3.500
Omnibus:	2.069	Durbin-Watson:	2.333			
Prob(Omnibus):	0.355	Jarque-Bera (JB):	1.176			
Skew:	0.357	Prob(JB):	0.555			
Kurtosis:	3.385	Cond. No.	61.2			

Figure 2.21: Results of a multiple linear regression between FA, tau accumulation in the isthmus cingulate cortex and the metabolism of the isthmus cingulate cortex.

Finally, having incorporated metrics and metabolism, additional multiple regression analyses were conducted to gauge the influence of other variables mentioned in the methods section. One such result is presented in Figure 2.22, indicating the model's significance and showcasing the predominant impact of isthmus cingulate tau pathology on the regression model. The tau pathology in the entorhinal cortex, however, exerts a lesser impact. After iteratively removing non-significant variables, the resulting essential factors are isthmus cingulate tau pathology and entorhinal cortex metabolism, as detailed in Figure 2.23.

Dep. Variable:	ctx_rh_isthmuscingulate_fdg_nopvc	R-squared:	0.508
Model:	OLS	Adj. R-squared:	0.354
Method:	Least Squares	F-statistic:	3.304
Date:	Tue, 08 Aug 2023	Prob (F-statistic):	0.00482
Time:	15:20:01	Log-Likelihood:	30.380
No. Observations:	43	AIC:	-38.76
Df Residuals:	32	BIC:	-19.39
Df Model:	10		
Covariance Type:	nonrobust		

	coef	std err	t	P> t	[0.025	0.975]
const	0.8756	0.680	1.287	0.207	-0.510	2.261
mean_FA_Cingulum_EHI_right	1.6827	0.877	1.920	0.064	-0.103	3.468
Age	-0.0038	0.004	-0.947	0.351	-0.012	0.004
Sex	-0.0627	0.050	-1.247	0.222	-0.165	0.040
Education	-0.0599	0.036	-1.658	0.107	-0.133	0.014
Beta_amyloid	5.792e-05	8.79e-05	0.659	0.515	-0.000	0.000
MMSE	0.0034	0.006	0.530	0.600	-0.010	0.017
apoe	-0.0336	0.051	-0.661	0.513	-0.137	0.070
ctx_rh_entorhinal_fdg_nopvc	0.2981	0.247	1.207	0.236	-0.205	0.801
ctx_rh_entorhinal_tau_pvc	-0.0100	0.031	-0.324	0.748	-0.073	0.053
ctx_rh_isthmuscingulate_tau_pvc	-0.1006	0.042	-2.399	0.022	-0.186	-0.015

Omnibus:	0.254	Durbin-Watson:	2.122
Prob(Omnibus):	0.881	Jarque-Bera (JB):	0.440
Skew:	-0.117	Prob(JB):	0.803
Kurtosis:	2.563	Cond. No.	2.88e+04

Notes:

[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.

[2] The condition number is large, 2.88e+04. This might indicate that there are strong multicollinearity or other numerical problems.

Figure 2.22: Results of a multiple linear regression between the metabolism of the isthmus cingulate cortex and all the parameters : FA in the second division of the cingulum, age, sex, education score, MMSE score, beta amyloid pathology, presence of the allele APOE4, entorhinal metabolism, entorhinal tau pathology and isthmus cingulate tau pathology.

OLS Regression Results						
Dep. Variable:	ctx_rh_isthmuscingulate_fdg_nopvc		R-squared:	0.408		
Model:	OLS		Adj. R-squared:	0.363		
Method:	Least Squares		F-statistic:	8.978		
Date:	Wed, 09 Aug 2023		Prob (F-statistic):	0.000120		
Time:	10:56:47		Log-Likelihood:	26.419		
No. Observations:	43		AIC:	-44.84		
Df Residuals:	39		BIC:	-37.79		
Df Model:	3					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
const	0.2821	0.324	0.870	0.390	-0.374	0.938
mean_FA_Cingulum_EHI_right	1.7048	0.659	2.588	0.013	0.373	3.037
ctx_rh_entorhinal_fdg_nopvc	0.4990	0.190	2.630	0.012	0.115	0.883
ctx_rh_isthmuscingulate_tau_pvc	-0.0997	0.036	-2.750	0.009	-0.173	-0.026
Omnibus:	1.090	Durbin-Watson:	2.133			
Prob(Omnibus):	0.580	Jarque-Bera (JB):	0.364			
Skew:	0.097	Prob(JB):	0.834			
Kurtosis:	3.407	Cond. No.	69.6			

Notes:

[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.

Figure 2.23: Results of a multiple linear regression between the metabolism of the isthmus cingulate cortex and following the parameters : FA in the second division of the cingulum, entorhinal metabolism and isthmus cingulate tau pathology.

2.2.2 DIAMOND analysis

Similar to the DTI model, the DIAMOND model also furnishes four metrics, elucidated in the preceding section: weighted axial diffusivity (**wAxD**), weighted radial diffusivity (**wRD**), weighted mean diffusivity (**wMD**), and weighted fractional anisotropy (**wFA**). Figure 2.24 visually represents the outcomes of the regressions. Once again, a greater significance is observed in the right hemisphere. However, unlike the DTI metrics, the control region does not appear to lack significance, a matter that will be addressed in subsequent discussions. Notably, the most prominent metrics in terms of significance within this model are **wRD** and **wMD**.

DIAMOND Regression results						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	wAxD cingulum first division	0,91749	⬆️	0,2573483	⬇️
Simple	fdg isthmus cingulate	wFA cingulum first division	0,1051	⬆️	0,1389227	⬆️
Simple	fdg isthmus cingulate	wMD cingulum first division	0,7475313	⬆️	0,0216321	⬇️
Simple	fdg isthmus cingulate	wRD cingulum first division	0,530542487	⬆️	0,03407	⬇️
Simple	fdg isthmus cingulate	wAxD cingulum second division	0,2943	⬆️	0,0189	⬇️
Simple	fdg isthmus cingulate	wFA cingulum second division	0,0284344	⬆️	0,03133	⬆️
Simple	fdg isthmus cingulate	wMD cingulum second division	0,08226	⬆️	0,0002688	⬇️
Simple	fdg isthmus cingulate	wRD cingulum second division	0,07885	⬆️	0,002094	⬇️
Simple	fdg isthmus cingulate	wAxD cingulum third division	0,24786	⬆️	0,13245	⬇️
Simple	fdg isthmus cingulate	wFA cingulum third division	0,02685	⬆️	0,03652	⬆️
Simple	fdg isthmus cingulate	wMD cingulum third division	0,04626987	⬆️	0,00226219	⬇️
Simple	fdg isthmus cingulate	wRD cingulum third division	0,0509767	⬆️	0,0123465	⬇️
Simple	fdg isthmus cingulate	wAxD uncinate fasciculus	0,000377	⬆️	0,0594	⬆️
Simple	fdg isthmus cingulate	wFA uncinate fasciculus	0,000537834	⬆️	0,00085647	⬆️
Simple	fdg isthmus cingulate	wMD uncinate fasciculus	0,4302	⬆️	0,2027	⬇️
Simple	fdg isthmus cingulate	wRD uncinate fasciculus	0,1392	⬆️	0,003884	⬇️

Figure 2.24: Results table of simple linear regressions between DIAMOND metrics and the metabolism of the isthmus cingulate cortex.

Upon segregating patients based on their amyloid status, the trends observed in Figure 2.25 in both hemispheres remain consistent, with limited impact on the significance of the DIAMOND metrics. The primary change is a reduction in significance, in comparison to the previous results.

DIAMOND Regression results with amyloid positif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	wAxD cingulum second division	0,3915	⬆️	0,24429	⬇️
Simple	fdg isthmus cingulate	wFA cingulum second division	0,08979	⬆️	0,1221	⬆️
Simple	fdg isthmus cingulate	wMD cingulum second division	0,1	⬆️	0,01499	⬇️
Simple	fdg isthmus cingulate	wRD cingulum second division	0,1226	⬆️	0,039	⬇️
DIAMOND Regression results with amyloid negatif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	wAxD cingulum second division	0,727	⬆️	0,051	⬇️
Simple	fdg isthmus cingulate	wFA cingulum second division	0,234	⬆️	0,16	⬆️
Simple	fdg isthmus cingulate	wMD cingulum second division	0,5335	⬆️	0,01531	⬇️
Simple	fdg isthmus cingulate	wRD cingulum second division	0,4789	⬆️	0,03818	⬇️

Figure 2.25: Results table of simple linear regressions between DIAMOND metrics and the metabolism of the isthmus cingulate cortex with amyloid population.

Moving to Figure 2.26, it appears that the introduction of entorhinal metabolism diminishes the significance of the DIAMOND metrics, particularly for the right hemisphere. However, the pattern of this table mirrors the behavior observed in the initial table.

DIAMOND Regression results										
Left Hemisphere						Right Hemisphere				
Metrics	Global P-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics	Global p-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics
wAxD 1	0,0168	0,005	0,859	↑	↑	0,00492	0,002	0,431	↑	↓
wFA 1	0,00439	0,004	0,101	↑	↑	0,00193	0,001	0,116	↑	↑
wMD 1	0,0163	0,005	0,766	↑	↓	0,00107	0,004	0,057	↑	↓
wRD 1	0,0137	0,004	0,51	↑	↓	0,00116	0,003	0,062	↑	↓
wAxD 2	0,0088	0,004	0,252	↑	↓	0,000776	0,003	0,039	↑	↓
wFA 2	0,00213	0,006	0,043	↑	↑	0,000979	0,002	0,051	↑	↑
wMD 2	0,00388	0,005	0,087	↑	↓	0,0000395	0,008	0,001	↑	↓
wRD 2	0,00432	0,005	0,099	↑	↓	0,00019	0,006	0,008	↑	↓
wAxD 3	0,00948	0,005	0,281	↑	↓	0,003	0,002	0,207	↑	↓
wFA 3	0,00215	0,007	0,043	↑	↑	0,00116	0,003	0,063	↑	↑
wMD 3	0,00299	0,006	0,064	↑	↓	0,000214	0,006	0,009	↑	↓
wRD 3	0,00323	0,006	0,07	↑	↓	0,000671	0,004	0,033	↑	↓
wAxD control	0,0000485	0,001	0,00001	↑	↑	0,000224	0,0001	0,01	↑	↑
wFA control	0,000195	0,023	0,003	↑	↑	0,0000917	0,006	0,004	↑	↑
wMD control	0,00476	0,002	0,112	↑	↑	0,00673	0,004	0,99	↑	↓
wRD control	0,0123	0,01	0,424	↑	↓	0,000864	0,016	0,044	↑	↓

Figure 2.26: Results table of multiple linear regressions between DIAMOND metrics, the metabolism of the entorhinal cortex and the isthmus cingulate cortex.

2.2.3 NODDI analysis

In the case of the NODDI model, a set of four metrics were retrieved: isotropic volume fraction (**fiso**), intracellular volume fraction (**fintra**), extracellular volume fraction (**fextra**), and orientation dispersion index (**ODI**). The outcomes obtained are graphically represented in Figures 2.27 and 2.29. Among these metrics, **fiso** and **fintra** demonstrate high levels of significance, while the remaining two metrics exhibit lower significance. Additionally, it's notable that the significance of **fiso** and **fintra** diminishes notably for the control region, especially when entorhinal metabolism is factored in.

Examining Figure 2.28, a clear trend emerges where the metrics **fintra** and **fextra** are more significant within the amyloid-positive population compared to others. The metrics demonstrates reduced overall significance when considering the entire population which aligns with the previous model.

NODDI Regression results						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	fiso cingulum first division	0,00128	↓	0,002051	↓
Simple	fdg isthmus cingulate	fintra cingulum first division	0,12319	↑	0,000493	↑
Simple	fdg isthmus cingulate	fextra cingulum first division	0,602	↑	0,314	↓
Simple	fdg isthmus cingulate	ODI cingulum first division	0,20884	↓	0,329785	↓
Simple	fdg isthmus cingulate	fiso cingulum second division	0,00012881	↓	0,0067	↓
Simple	fdg isthmus cingulate	fintra cingulum second division	0,027487	↑	0,000055145	↑
Simple	fdg isthmus cingulate	fextra cingulum second division	0,70635	↓	0,025699	↓
Simple	fdg isthmus cingulate	ODI cingulum second division	0,20951834	↓	0,279705	↓
Simple	fdg isthmus cingulate	fiso cingulum third division	0,00001022	↓	0,001205	↓
Simple	fdg isthmus cingulate	fintra cingulum third division	0,0082899	↑	0,000509159	↑
Simple	fdg isthmus cingulate	fextra cingulum third division	0,3769	↓	0,04532	↓
Simple	fdg isthmus cingulate	ODI cingulum third division	0,16777	↓	0,1499581	↓
Simple	fdg isthmus cingulate	fiso uncinate fasciculus	0,743496	↓	0,07289	↓
Simple	fdg isthmus cingulate	fintra uncinate fasciculus	0,6407	↑	0,0401	↑
Simple	fdg isthmus cingulate	fextra uncinate fasciculus	0,8734	↓	0,4625	↓
Simple	fdg isthmus cingulate	ODI uncinate fasciculus	0,0066	↓	0,0212	↓

Figure 2.27: Results table of simple linear regressions between NODDI metrics and the metabolism of the isthmus cingulate cortex.

NODDI Regression results with amyloid positif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	fiso cingulum second division	0,016339	↓	0,21	↓
Simple	fdg isthmus cingulate	fintra cingulum second division	0,04643	↑	0,001536	↑
Simple	fdg isthmus cingulate	fextra cingulum second division	0,35	↓	0,0158789	↓
Simple	fdg isthmus cingulate	ODI cingulum second division	0,45654	↓	0,47389	↓

NODDI Regression results with amyloid negatif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	fiso cingulum second division	0,00598	↓	0,01996	↓
Simple	fdg isthmus cingulate	fintra cingulum second division	0,3749	↑	0,0255	↑
Simple	fdg isthmus cingulate	fextra cingulum second division	0,653535	↓	0,45184	↓
Simple	fdg isthmus cingulate	ODI cingulum second division	0,22051	↓	0,32268	↓

Figure 2.28: Results table of simple linear regressions between NODDI metrics and the metabolism of the isthmus cingulate cortex with amyloid population.

NODDI Regression results										
Left Hemisphere						Right Hemisphere				
Metrics	Global P-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics	Global p-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics
fiso 1	0,000259	0,013	0,004	↑	↓	0,0000955	0,003	0,004	↑	↓
fintra 1	0,00717	0,006	0,19	↑	↑	0,0000591	0,007	0,002	↑	↑
fextra 1	0,0149	0,005	0,603	↑	↑	0,00524	0,002	0,482	↑	↓
ODI 1	0,00547	0,003	0,134	↑	↓	0,00451	0,002	0,374	↑	↓
fiso 2	0,0000128	0,005	0,0001	↑	↓	0,000105	0,001	0,004	↑	↓
fintra 2	0,00201	0,006	0,04	↑	↑	0,0000114	0,01	0,0001	↑	↑
fextra 2	0,0165	0,005	0,8	↑	↑	0,00167	0,005	0,097	↑	↑
ODI 2	0,00631	0,004	0,161	↑	↓	0,00436	0,002	0,355	↑	↓
fiso 3	0,0000165	0,007	0,0001	↑	↓	0,0000193	0,001	0,001	↑	↓
fintra 3	0,000935	0,008	0,017	↑	↑	0,000085	0,009	0,003	↑	↑
fextra 3	0,0135	0,005	0,496	↑	↑	0,00252	0,005	0,164	↑	↑
ODI 3	0,00655	0,004	0,169	↑	↓	0,00272	0,002	0,181	↑	↓
fiso control	0,017	0,005	0,939	↑	↓	0,00221	0,003	0,138	↑	↓
fintra control	0,0159	0,005	0,71	↑	↓	0,00362	0,008	0,268	↑	↑
fextra control	0,0162	0,004	0,746	↑	↑	0,0067	0,002	0,933	↑	↑
ODI control	0,000296	0,003	0,005	↑	↓	0,000339	0,001	0,015	↑	↓

Figure 2.29: Results table of multiple linear regressions between NODDI metrics, the metabolism of the entorhinal cortex and the isthmus cingulate cortex.

2.2.4 Microstructure Fingerprinting analysis

For the final model, two metrics were extracted: total fiber volume fraction (**fvf_tot**) and weighted fiber volume fraction (**wfvf**). Interestingly, **fvf_tot** ap-

pears to hold significance across the three divisions of the cingulum as shown on the Figure 2.30, yet it lacks significance in the control region. On the other hand, **wfvf** appears to be non-significant. However, with the inclusion of entorhinal metabolism on the Figure 2.32, the significance of the metrics from the MF model declines, suggesting that this model might not effectively address the research question. A more comprehensive discussion of these observations will be presented later.

When assessing the impact of splitting the amyloid status population, the trends observed align with those of the three previous models as observed on the Figure 2.31.

MF Regression results						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	fvf_tot cingulum first division	0,478	⬆️	0,00214	⬇️
Simple	fdg isthmus cingulate	wfvf cingulum first division	0,41741978	⬇️	0,364697	⬆️
Simple	fdg isthmus cingulate	fvf_tot cingulum second division	0,117645	⬆️	0,00568499	⬆️
Simple	fdg isthmus cingulate	wfvf cingulum second division	0,6538	⬆️	0,0674	⬆️
Simple	fdg isthmus cingulate	fvf_tot cingulum third division	0,04678	⬆️	0,01961	⬆️
Simple	fdg isthmus cingulate	wfvf cingulum third division	0,29908	⬆️	0,1144589	⬆️
Simple	fdg isthmus cingulate	fvf_tot uncinate fasciculus	0,54735	⬆️	0,146796	⬆️
Simple	fdg isthmus cingulate	wfvf uncinate fasciculus	0,67034	⬆️	0,3544754	⬆️

Figure 2.30: Results table of simple linear regressions between MF metrics and the metabolism of the isthmus cingulate cortex.

MF Regression results with amyloid positif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	fvf_tot cingulum second division	0,087	⬆️	0,01937	⬆️
Simple	fdg isthmus cingulate	wfvf cingulum second division	0,395	⬆️	0,08298	⬆️

MF Regression results with amyloid negatif patients						
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right
Simple	fdg isthmus cingulate	fvf_tot cingulum second division	0,725	⬆️	0,1686	⬆️
Simple	fdg isthmus cingulate	wfvf cingulum second division	0,7529	⬇️	0,4396	⬆️

Figure 2.31: Results table of simple linear regressions between MF metrics and the metabolism of the isthmus cingulate cortex with amyloid population.

MF Regression results										
Left Hemisphere						Right Hemisphere				
Metrics	Global P-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics	Global p-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics
fvf_tot 1	0,0146	0,005	0,579	⬆️	⬆️	0,0008	0,003	0,04	⬆️	⬆️
wfvf 1	0,0131	0,005	0,471	⬆️	⬇️	0,00457	0,002	0,383	⬆️	⬆️
fvf_tot 2	0,00675	0,006	0,176	⬆️	⬆️	0,000488	0,006	0,023	⬆️	⬆️
wfvf 2	0,0161	0,005	0,736	⬆️	⬆️	0,00239	0,003	0,152	⬆️	⬆️
fvf_tot 3	0,00309	0,006	0,066	⬆️	⬆️	0,00109	0,004	0,058	⬆️	⬆️
wfvf 3	0,0102	0,005	0,313	⬆️	⬆️	0,00327	0,003	0,232	⬆️	⬆️
fvf_tot control	0,017	0,006	0,958	⬆️	⬇️	0,00569	0,004	0,566	⬆️	⬆️
wfvf control	0,017	0,005	0,914	⬆️	⬇️	0,00661	0,003	0,854	⬆️	⬆️

Figure 2.32: Results table of multiple linear regressions between MF metrics, the metabolism of the entorhinal cortex and the isthmus cingulate cortex.

2.2.5 Tractography analysis

The outcome of constructing the tractogram crossing the entorhinal cortex, the second division of the cingulum bundle, and the posterior cingulate cortex is illustrated in Figure 2.33. This personalized tractogram was generated for each patient in the dataset, incorporating the fiber count into the dataset as well. A linear regression was subsequently performed to investigate whether the number of fibers within this region has any impact on the potential metabolism of the isthmus cingulate cortex. Figure 2.34 showcases the results of the linear regression involving only the fiber count and the metabolism of the isthmus cingulate cortex. On the other hand, Figure 2.35 presents the outcomes when the entorhinal cortex metabolism is included. In both cases, the results indicate that the number of fibers is not a variable that can predict the metabolism of the isthmus cingulate cortex.

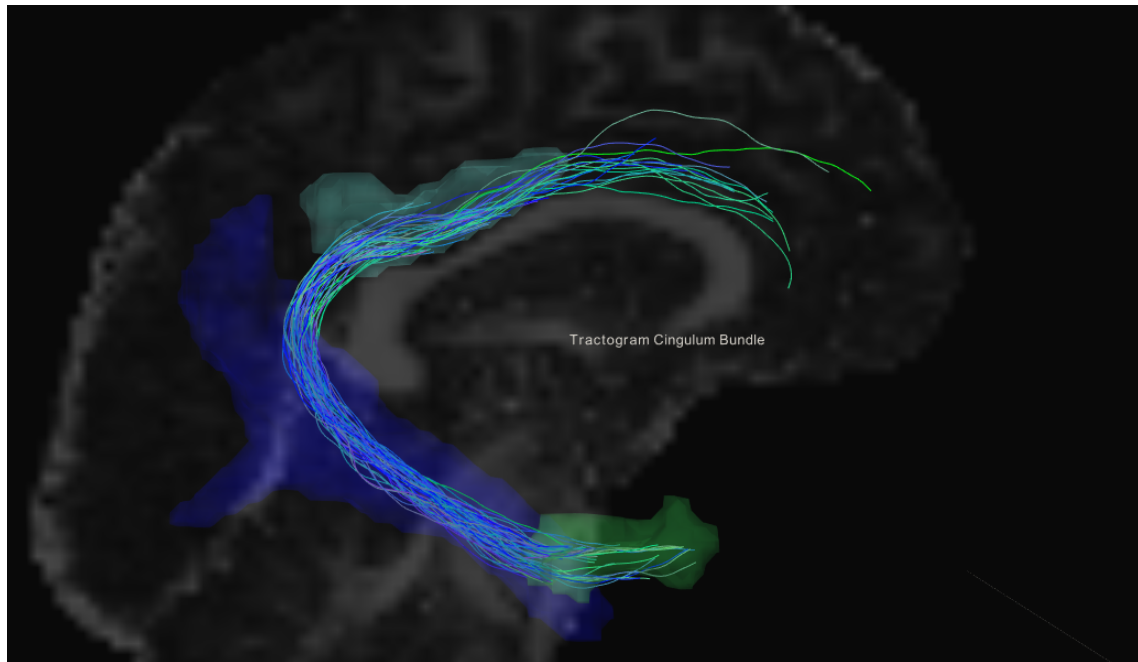


Figure 2.33: Tractogram of the cingulum bundle in the right hemisphere for the patient 9. In green the entorhinal cortex, in blue the second division of the cingulum and in light blue the posterior cingulate cortex. The FA map of the patient can be seen in the background.

Track count Regression results							
Type	Dependent variable	Other variables	P-value left hemisphere	Tendency left	P-value right hemisphere	Tendency right	
Simple	fdg isthmus cingulate	track count	0,529	↑	0,131	↑	

Figure 2.34: Results table of simple linear regressions between track count and the metabolism of the isthmus cingulate cortex.

Track count regression results											
Left Hemisphere						Right Hemisphere					
Metrics	Global P-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics	Global p-value	fdg p-value	Metrics p-value	Tendency fdg	Tendency metrics	
track count	0,0102	0,003	0,764	↑	↑	0,00729	0,006	0,401	↑	↑	

Figure 2.35: Results table of multiple linear regressions between track count, the metabolism of the entorhinal cortex and the isthmus cingulate cortex.

2.3 Discussion

Within this section, a comprehensive analysis of the outcomes presented in the preceding section will be undertaken. The objective is to provide an interpretation of the results and address the central research question: What is the association between the cingulum bundle connectivity and the posterior cingulate metabolism ? A subsequent subsection will succinctly summarize the discussed results and offer a conclusive answer to the research inquiry.

2.3.1 Relevance of the microstructural models

A coherence analysis was conducted to highlight the consistency between various metrics within each model and across metrics from different models. These analyses serve to critically assess the models' validity and the confidence in their outcomes.

The first analysis pertained to the NODDI metrics: **fiso**, **fintra**, and **fextra**. These metrics should ideally sum up to one in each voxel, considering the nature of their definitions. To validate this, the equation:

$$fiso + fintra + fextra = 1 \quad (2.3)$$

was evaluated for each ROI mentioned in the results section. A percentage was then calculated, indicating the proportion of values equal to one versus those that differed for each patient. The average percentage was determined for each ROI. Remarkably, in the case of NODDI metrics, a 100% consistency was achieved across all ROIs, indicating that the different fractions indeed balanced each other.

For the MF model, similar analysis was performed on the fractions **frac_csf** and **frac_ftot**, which should sum up to one:

$$frac_csf + frac_ftot = 1. \quad (2.4)$$

As before, a 100% consistency was observed for each ROI, confirming the coherence of this model as well, and thus reinforcing the reliability of the values it provides.

However, the analysis took a different turn for the DIAMOND model. The equation :

$$frac_f0 + frac_f1 + frac_csf = 1 \quad (2.5)$$

was tested, where **frac_f0** represents the fraction of fibers from population 0 and **frac_f1** is the fraction of fibers from population 1. The percentage analysis revealed that a perfect 100% consistency was not achieved for any ROI, as seen in the following results:

- First division of the Cingulum left : 99.74723308828759%
- First division of the Cingulum right : 99.74293750794135%
- Second division of the Cingulum left : 99.81310134983686%
- Second division of the Cingulum right : 99.81419063858831%
- Third division of the Cingulum left : 99.91666456223834%
- Third division of the Cingulum right : 99.90946188412639%
- Uncinate Fasciculus left : 98.85831106612645%
- Uncinate Fasciculus right : 98.72947554176869%

Although the diamond fractions of fiber populations didn't exhibit complete compensation, the high percentage of values that did align still suggests the relevance of the values obtained from the DIAMOND model.

Furthermore, relationships between metrics from different models were explored, such as **FA**, **wFA**, and **ODI**. **FA** and **wFA** should exhibit similar behavior : When **FA** values increase, **wFA** values should also increase. Conversely, **ODI**, representing fiber orientation dispersion, should decrease as **FA** increases, reflecting a contrasting concept. This relationship was consistently observed in the results presented in Figures 2.17, 2.24, and 2.27. The color-coded arrows, when green and upward for **FA** and **wFA**, are red and downward for **ODI**. They confirm these relationships, further validating the coherence of these metrics.

Finally, while the metrics from DTI and DIAMOND are conceptually similar, the latter considers crossing fiber populations. Therefore, it is coherent that when, for instance, **FA** increases, **wFA** should also increase. A comparison between Figures

2.17 and 2.24 affirms that, when statistically significant, the metrics follow similar trends. These observations establish the coherence and consistency of these models. However, as DIAMOND was devised to address the limitations of DTI, the differences in their values are expected, underscoring the enhanced relevance of the DIAMOND model.

2.3.2 Interpretation of the results

Upon a detailed examination of the results, an initial and prominent observation from Figure 2.14 is that the entorhinal metabolism serves as a robust predictor of isthmus cingulate metabolism. This relationship is quite evident, but delving deeper is essential to comprehend the underlying dynamics and potential factors influencing this connection. A subsequent analysis, presented in Figure 2.15, was conducted to investigate whether tau pathology plays a role in shaping this primary association. The findings indicate that tau pathology within the isthmus cingulate effectively predicts its own metabolism, while tau pathology in the entorhinal cortex does not exhibit a comparable predictive relationship. At this juncture, two key parameters seem to underlie the metabolism of the isthmus cingulate cortex: entorhinal cortex metabolism and tau accumulation within the isthmus cingulate.

Another insightful analysis revealed that the FCSRT Free Recall score can indeed account for isthmus cingulate cortex metabolism, but notably, this holds true only for the left hemisphere. What precisely does the FCSRT Free Recall variable entail? The acronym "FCSRT" stands for "Free and Cued Selective Reminding Test," a diagnostic tool in Alzheimer's disease assessment. As elaborated in the article [40], the FCSRT effectively differentiates typical Alzheimer's disease from other conditions, such as Lewy body disease or frontotemporal dementia. The test evaluates the ability to learn a set of 16 written words presented with semantic cues to control memory encoding. Memory recall is assessed through spontaneous retrieval ("free recall") and retrieval aided by semantic cues for unrecalled items ("total recall" = "free recall" + "cued recall"). The procedure is repeated after 30 minutes to assess "delayed free recall" and "delayed total recall." Another study demonstrated that certain FCSRT variables, like "delayed total recall" and "number of intrusions," prove to be the most discriminative indicators, showing strong dependence on hippocampal region hypometabolism [41].

Consequently, this analysis aimed to ascertain whether FCSRT scores correlate with isthmus cingulate metabolism. However, as depicted in Figure 2.16, the results do not establish a definitive correlation. While a mild significance is observed in the left hemisphere, it's crucial to note that "Free recall" is not inherently linked to

isthmus cingulate metabolism. As a result, these variables were not pursued further, given their inability to serve as predictors for metabolism in this region. For the entorhinal region, "free recall" and "delayed free recall" exhibit slight significance (p-value equal to 0.05) in the left region, yet this level of significance remains insufficient to confidently predict subsequent outcomes.

DTI analysis and interpretation

To provide a quick recap, the four metrics originating from the DTI model hold the following meanings: mean diffusivity, which indicates white matter damage; radial diffusivity, possibly reflecting myelin disruption; axial diffusivity, more specific to axonal degeneration or loss; and fractional anisotropy, an indirect measure of axonal integrity and fiber packing within a voxel.

The initial noteworthy observation pertains to the divergence in significant p-values between the left and right hemispheres. Interestingly, all values exhibit greater significance in the right hemisphere. This observation aligns with findings from the foundational article underpinning this master thesis [21], and remains consistent for metrics computed using other models as well. The second notable observation stems from the realization that within the right hemisphere, all metrics are relevant except for axial diffusivity (AxD), aligning with prior conclusions in [21]. In the left hemisphere, only fractional anisotropy (FA) and radial diffusivity (RD) are relevant in the second and third divisions of the cingulum.

These observations suggest that axonal degeneration or loss does not serve as a predictor for isthmus cingulate metabolism. Conversely, fiber packing within a voxel, white matter damage, and myelin disruption could play roles in influencing this metabolism. Given that entorhinal metabolism predicts isthmus cingulate metabolism, introducing these metrics as covariates reveals that in the right hemisphere, only FA and RD for the first division of the cingulum, and FA, RD, and mean diffusivity (MD) for the remaining divisions are significant. In the left hemisphere, only FA in the third division of the cingulum holds significance. It is matching the results found by Mayo et al. [14] where the HCB exhibited low FA values and high MD. The direct relationship between FA, entorhinal metabolism, and metabolism in the isthmus cingulate suggests that reduced fiber packing results in decreased metabolism in the isthmus cingulate. Conversely, the inverse correlation between MD and RD may account for reduced metabolism in this area, indicating the presence of white matter damage and myelin disruption as explanatory factors.

The metrics likely achieve higher significance in the second and third divisions

due to their inclusion of portions of the isthmus cingulate, whereas the first division concludes just before this region.

Within the control region, only FA in the left hemisphere exhibits slight significance. This could be connected to the outcomes of Fujie et al. [15], which established a connection between reduced FA values and the precision of facial expression recognition in individuals with amnesic MCI. These findings reveal underlying issues in memory and emotional processing among the amnesic MCI group. Therefore, given the correlation between PCC hypometabolism and cognitive decline [42], and the positive correlation between FA values and metabolism in the isthmus cingulate cortex, a similar interpretation can be drawn in this context.

As detailed in the results, it's evident from Figure 2.19 that metrics exhibit greater relevance in patients displaying amyloid- β deposition. This significance extends to FA, MD, and RD metrics in the right hemisphere, corroborating earlier findings. However, for patients devoid of amyloid- β deposition, these metrics do not maintain significance. This implies a potential association between metrics and amyloid- β deposition. Yet, the deposition does not appear to predict isthmus cingulate metabolism, as indicated in Figure 2.22, where the p-value for this variable stands at 0.515.

Given the established link between tau tangles accumulation and metabolism, isthmus cingulate tau tangles accumulation emerges as a valuable predictor of its metabolism, alongside the entorhinal cortex metabolism. The outcomes involving DTI metrics demonstrate that even in cases where metrics aren't significant, these two predictors retain their significance. Notably, in instances where MD and RD are significant in the second division of the right hemisphere's cingulum, in conjunction with the complete set of covariables, tau tangles accumulation also exhibits significance.

Factors like gender, education score, MMSE score, and APOE4 allele presence don't seem to impact the regression outcomes. However, age appears to be a predictor alongside tau tangles accumulation in the left hemisphere. This result has also been observed in the study from Scheltens et al. [42]. Subsequently, with the inclusion of age, DTI metrics lose significance, save for FA.

DIAMOND analysis and interpretation

While the DIAMOND model alleviates the limitations of DTI, resulting in metrics with consistent meanings, the outcomes differ. The right hemisphere tendency

remains apparent. In the right hemisphere, the **wMD** and **wRD** for the first division of the cingulum are significant. Similarly, for the second division, the **wAxD**, **wFA**, **wMD**, and **wRD** metrics display significance. In contrast, only **wAxD** is insignificant for the third division. For the left hemisphere, the first division lacks significance, with only **wFA** proving significant for the second and third divisions.

Notably, the left hemisphere's uncinate fasciculus exhibits significance in **wAxD** and **wFA**, while the right hemisphere displays significance in **wFA** and **wRD**. As with the DTI model, **wFA**, **wMD**, and **wRD** once again emerge as the most significant metrics, suggesting a link between metabolism and white matter integrity. Incorporating entorhinal metabolism as a covariable yields only slight deviations in results. The first division remains insignificant, likely due to its lack of inclusion of the isthmus cingulate cortex. For the second division, outcomes remain consistent, and while for the third division, formerly significant metrics exhibit slightly reduced significance. In the control region **wAxD** becomes significant in both hemisphere. The significance of the control region's metrics could be attributed to the presence of fiber packing, myelin disruption, or deletion, aligning with behaviors seen in the second division of the cingulum. Conversely, **wMD**, significant in the second division, becomes insignificant in the control region, indicating distinct behavior in white matter damage between the two.

Thus, the relation with connectivity between the entorhinal and the isthmus cingulate and metabolism is evident. It also confirms the results obtained with DTI model. Therefore, the overall diffusivity between the entorhinal and isthmus cingulate may serve as an indicator for explaining metabolism in the isthmus cingulate.

Upon segregating patients based on amyloid- β deposition, no discernible distinction emerged in the metrics for this model, suggesting an absence of connection with amyloid- β .

Employing a robust regression involving age, gender, amyloid- β deposition, MMSE score, Education score, and presence of the APOE4 allele, the significance of **wMD** and **wRD** persists as predictors of isthmus cingulate metabolism. Sequentially eliminating variables corroborates the outcome from DTI analysis. Age could impact left hemisphere metabolism alongside tau tangles accumulation, while in the right hemisphere, entorhinal metabolism with isthmus cingulate tau tangles accumulation prevails.

NODDI analysis and interpretation

The NODDI model, much like the DIAMOND model, accounts for distinct fiber populations. The four metrics derived from this model can provide insights into white matter integrity. Firstly, **fintra** indicates the proportion of the voxel occupied by the intra-cellular compartment, reflecting fiber volume changes. An increase in **fintra** could signify axonal regrowth or swelling due to inflammation. Conversely, a decrease might result from axonal degeneration, deletion, or inflammation affecting the extra-axonal space represented by **fextra**. Additionally, **fextra** signifies the extra-cellular compartment, indicating high-quality myelin or inflammation-induced swelling. **Fiso** represents the CSF compartment with fully isotropic diffusion, while **ODI** ranges from 0 to 1, inversely reflecting fiber alignment, analogous to **FA** in previous models.

Considering these insights, the obtained results highlighted the significance of **fiso** and **fintra**, especially in the second and third divisions of the cingulum for both hemispheres. This significance persists even when accounting for entorhinal metabolism. **Fiso** tends to decrease with increased metabolism in the isthmus cingulate, while **fintra** tends to increase, suggesting that higher metabolism corresponds to more intra-cellular compartment volume. This implies a relationship where increased metabolism in the isthmus cingulate aligns with metabolism in the entorhinal cortex and a greater fraction of intra-cellular compartment volume. Conversely, when the CSF fraction is higher, connectivity and metabolism from the entorhinal to the isthmus cingulate decrease. This confirms results from Fu et al. [16] where **fiso** was found to be high in MCI and AD groups. According to Colgan et al. [18], it is indicating cell shrinkage and decreased tissue volume fraction, thus atrophy. However, while **fiso** and **fintra** are significant, **fextra** should also be significant, given their sum equals one, as discussed in section 2.3.1. Interestingly, **fextra** is significant only in the right hemisphere for the second and third divisions of the cingulum, once again indicating hemisphere-specific differences.

The amyloid- β population segregation did not yield distinct patterns. **Fiso** was significant in the left hemisphere for the amyloid- β positive group and in both hemispheres for the other group. **Fintra** and **fextra** were significant for the first group, but not for the second. The results did not reveal a clear trend.

Performing robust regression by including additional parameters as covariates affirmed the relevance of **fiso**, **fintra**, and occasionally **fextra**. However, the regression models maintained the same trends observed in the previous analyses with DTI and DIAMOND metrics. In the left hemisphere, age appeared to correlate with metabolism, while in the right hemisphere, entorhinal cortex metabolism

remained significant.

MF analysis and interpretation

Similar to the DIAMOND model, the MF model also accommodates various fiber populations. The retrieved metrics, namely `wfvf` and `fvf_tot`, as discussed in section 2.1.4, encapsulate slightly distinct meanings. `wfvf` quantifies the fiber proportion in compartments, while `fvf_tot` considers this proportion across the entire voxel, omitting the CSF compartment.

In the context of the results, these metrics are insignificant for the entire left hemisphere. However, `fvf_tot` exhibits significance in the right hemisphere for all three divisions of the cingulum. This observation suggests that the CSF compartment holds information related to the isthmus cingulate metabolism. Conversely, in the control region, none of the metrics prove to be relevant. With entorhinal metabolism included as a covariate, the significance of `fvf_tot` persists. This outcome aligns with the findings of the NODDI model, where the `fiso` metric, representing the fiber fraction in the CSF compartment, proved to be a meaningful predictor of metabolism. Consequently, the MF model reaffirms this trend.

Examining the segregation based on amyloid status, only `fvf_tot` emerges as a significant metric in the right hemisphere when amyloid- β accumulation is present. This may indicate a subtle impact of this accumulation, although insufficient for drawing conclusive inferences.

Robust regression reaffirms that only `fvf_tot` retains significance, specifically for the right hemisphere. The trends observed with covariables remain consistent with those in the three preceding models.

2.3.3 Tractography analysis

The outcomes derived from tractography yielded no significant findings. Consequently, the quantity of fibers present within the tractogram does not serve as an indicator capable of elucidating the metabolism within the isthmus cingulate. This lack of significance persists even after applying robust regression. This outcome likely implies that the pivotal factor is not the number of fibers per se, but rather the overall integrity of each individual fiber.

2.3.4 Association between the cingulum bundle connectivity and the posterior cingulate metabolism : synthesis

Drawing upon the insights presented in the articles discussed in Section 1.2.4, a series of research inquiries were formulated, investigated, and analyzed. This synthesis culminates in a comprehensive response to these inquiries.

The central research question focused on elucidating the primary factors underlying hypometabolism within the posterior cingulate cortex. To address this question, the study concentrated on the isthmus cingulate, a component of the posterior cingulate cortex, utilizing data from 45 patients spanning from MCI and AD dementia. The results and ensuing discussions has revealed that multiple factors contribute to this metabolism.

Firstly, a direct association exists between the accumulation of tau tangles within the same region and metabolic changes. However, the accumulation of tau tangles in the entorhinal cortex does not serve as a predictive factor for this hypometabolism.

Secondly, the metabolic activity in the entorhinal cortex is related with the metabolism in the isthmus cingulate. The interplay between these two regions was scrutinized and uncovered that the connectivity between them has an impact on isthmus cingulate metabolism. This connectivity's influence varies across hemispheres. Notably, the right hemisphere displays a more substantial impact on the relationship while in the left hemisphere the age appeared to be another predictor of this relation. Connectivity disruption, stemming from myelin degradation and white matter damage, significantly influences the isthmus cingulate's metabolic state. As the integrity of the connecting fibers diminishes, the metabolic activity in the isthmus cingulate decreases as well. Additionally, the declining fraction of the intra-cellular compartment within fibers contributes to decreased connectivity and subsequently, decreased metabolism. The metrics derived from DTI and NODDI analyses corroborated previous findings, while the DIAMOND and MF metrics validated the observed trends. However, it's noteworthy that the tractography analysis established that the number of fibers within the tractogram between the entorhinal and isthmus cingulate does not exert a discernible impact on this relationship.

Finally, variables such as gender, MMSE score, FCSRT score, education score, APOE4 allele and accumulation amyloid- β seems to not influence the connectivity and the metabolism in the isthmus cingulate.

2.3.5 Limitations

One of the primary limitations of this thesis arises from the inability to execute all preprocessing steps in their entirety. A significant portion of this preprocessing procedure was left unperformed, and the resultant outcomes must be evaluated with this in mind. Moreover, the analysis hinged on atlas maps originating in their own spatial contexts, which were subsequently translated into the individual spaces of each patient. This approach introduces the potential for minor patient movements to inadvertently influence region of interest selection. Although patient movements were seemingly minimal, their potential impact should not be dismissed. Consequently, while extensive verification of each region was conducted for a substantial proportion of patients, it wasn't feasible to perform this meticulous process for all patients due to its manual nature. The registration is for its part automated.

Another constraint closely associated with atlases is their probabilistic nature, implying that unintentional inclusion of segments from neighboring regions might have occurred within each defined region. Furthermore, given that the study focused on individuals with MCI or AD, whose brains are affected by the disease, the regions under consideration could already be subject to damage. Consequently, the registration process might encompass portions of adjoining regions due to the lack of precise delimitation.

Then, the subdivision of the cingulum bundle into distinct sections is a subjective decision, driven by the desire to encompass regions of interest. This division process was carried out using MRICroGL software [43] to obtain initial coordinates, followed by manual refinement using Python. It's important to acknowledge that a degree of error might be inherent in these divisions, possibly impacting their significance, which warrants further discussion.

Furthermore, it's crucial to note that the interpretation of the obtained metrics is inherently subjective. This subjectivity is highlighted in various studies, with metrics such as ODI exhibiting diverse trends depending on the specific research context. Therefore, the interpretation offered by different authors can vary. Similarly, the interpretation of the metrics conducted within this master's thesis remains subjective, despite certain results aligning with prior research findings.

Finally, the construction of the tractogram during the tractography analysis has been made using the atlases. Therefore, for the same reasons mentioned above about errors from registration, the tractogram of each patient could contain more or less the right number of fibers. As the number of fibers is not elevated, an error could lead to erroneous results and interpretations.

2.3.6 Further perspectives

There are many limitations, one that have not been mentioned pertained to the limitation of time. The challenges encountered during preprocessing resulted in significant time loss. The data hold potential for conducting supplementary analyses and adjustments to some of the ongoing analyses. Therefore, it is evident that there remains a considerable scope for further investigation using this dataset to enhance the understanding of hypometabolism within the posterior cingulate cortex.

Firstly, the grey matter was not studied in this report, but it could provide some additional information about the microstructural changes in the cortexes. Although some models such as DIAMOND might not give accurate results in the grey matter, the microstructural changes within the entorhinal cortex or the isthmus cingulate cortex could be an interesting added value to the study.

Furthermore, there is potential for conducting supplementary investigations using different datasets to validate or deny the findings and extend the discourse. Moreover, the implementation of a longitudinal study could offer insights into the progression of connectivity between the entorhinal cortex and the isthmus cingulate, shedding light on whether the correlation between connectivity and hypometabolism is inherent, whether the connectivity evolves along with the metabolism or if it emerges as a consequence of AD.

Finally, the utilization of microstructural models in this study is based on relatively recent advancements, and the number of studies delving into these models within the existing literature remains limited. Particularly, DIAMOND and MF exhibit a low amount of literature concerning their application. This poses a constraint on the comprehensive interpretation of these metrics and the potential combinations across all the models, as their full comprehension within the scientific community is still evolving. Consequently, it is the diversity of researches, specifically focusing on these novel models, that will contribute to enhancing the broader understanding of their metrics and ultimately providing clarity on their appropriate interpretation.

2.4 Conclusion

Alzheimer’s disease remains a significant societal concern due to the absence of effective pharmacological interventions to prevent or slow its progression. As a result, there is a pressing need to enhance comprehension of this pathology and the underlying mechanisms driving it. Researchers are actively engaged in investigating these intricate mechanisms to expand our knowledge of the disease, a pursuit shared by this master’s thesis.

Prior researchs have highlighted hypometabolism within the posterior cingulate cortex as a hallmark of Alzheimer’s disease. To further understand this phenomenon, anatomical and diffusion MRI images were obtained from a cohort of 65 patients spanning from MCI to AD dementia. These data underwent preprocessing using ElikoPy, and subsequently, microstructural models encompassing DTI, DIAMOND, NODDI, and MF were employed to quantify diverse parameters. Each model’s metrics carry distinct interpretations and were applied to the white matter of various regions of interest. A subsequent statistical analysis employing robust linear regression was performed.

The noteworthy findings highlighted a direct association between the connectivity of the cingulum bundle which links the entorhinal cortex and the isthmus cingulate that lies within the posterior cingulate cortex, and its metabolism. This connection was particularly pronounced within the right hemisphere, whereas in the left hemisphere, patient age emerged as a significant factor. These observed metric trends were interpreted as indicative of connectivity disruption, attributed to myelin degradation and white matter damage. Another intriguing discovery was that tau tangle accumulation within the isthmus cingulate predicted its metabolism, unlike the accumulation in the entorhinal cortex, which did not. Thus, the connectivity between these two regions appears not to influence tau pathology. These conclusions were coherent with previous findings.

However, it’s important to acknowledge certain limitations of the study. For instance, preprocessing setbacks had an impact, leading to the omission of certain steps and potentially introducing errors into the results.

Despite these limitations, the results of this study exhibits informations about the association between the connectivity of the cingulum bundle and the posterior cingulate hypometabolism. Therefore, this work contribute to the understanding of the mechanisms underlying the Alzheimer’s disease and even provide further perspectives to improve it.

Bibliography

- [1] *En chiffres*. fr-FR. URL: <https://alzheimer.be/la-maladie-dalzheimer/en-chiffres/> (visited on 05/06/2023).
- [2] Bruno Dubois et al. “Clinical diagnosis of Alzheimer’s disease: recommendations of the International Working Group”. In: *The Lancet Neurology* 20.6 (June 2021), pp. 484–496. ISSN: 14744422. DOI: 10.1016/S1474-4422(21)00066-1. URL: <https://linkinghub.elsevier.com/retrieve/pii/S1474442221000661> (visited on 10/30/2022).
- [3] B. Kastler and P. Anstett. *Comprendre l’IRM: manuel d’auto-apprentissage*. 7ème éd. entièrement rév. OCLC: 787845294. Issy-les-Moulineaux [France]: Elsevier Masson, 2011. ISBN: 978-2-294-72168-7.
- [4] Andrew L Alexander et al. “Diffusion tensor imaging of the brain”. In: *DIFFUSION TENSOR IMAGING* 4.3 (2007), p. 14.
- [5] Kenichi Oishi et al. “DTI Analyses and Clinical Applications in Alzheimer’s Disease”. In: *Journal of Alzheimer’s Disease* 26 (s3 Oct. 4, 2011). Ed. by J. Wesson Ashford et al., pp. 287–296. ISSN: 18758908, 13872877. DOI: 10.3233/JAD-2011-0007. URL: <https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/JAD-2011-0007> (visited on 10/20/2022).
- [6] Hui Zhang et al. “NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain”. In: *NeuroImage* 61.4 (July 2012), pp. 1000–1016. ISSN: 10538119. DOI: 10.1016/j.neuroimage.2012.03.072. URL: <https://linkinghub.elsevier.com/retrieve/pii/S1053811912003539> (visited on 12/12/2022).
- [7] Benoit Scherrer et al. “Characterizing brain tissue by assessment of the distribution of anisotropic microstructural environments in diffusion-compartment imaging (DIAMOND): Characterizing Brain Tissue with DIAMOND”. In: *Magnetic Resonance in Medicine* 76.3 (Sept. 2016), pp. 963–977. ISSN: 07403194. DOI: 10.1002/mrm.25912. URL: <https://onlinelibrary.wiley.com/doi/10.1002/mrm.25912> (visited on 12/12/2022).

-
- [8] Gaëtan Rensonnet et al. “Towards microstructure fingerprinting: Estimation of tissue properties from a dictionary of Monte Carlo diffusion MRI simulations”. In: *NeuroImage* 184 (Jan. 2019), pp. 964–980. ISSN: 10538119. DOI: 10.1016/j.neuroimage.2018.09.076. URL: <https://linkinghub.elsevier.com/retrieve/pii/S1053811918319487> (visited on 12/12/2022).
 - [9] William Jagust. “Imaging the evolution and pathophysiology of Alzheimer disease”. In: *Nature Reviews Neuroscience* 19.11 (Nov. 2018), pp. 687–700. ISSN: 1471-003X, 1471-0048. DOI: 10.1038/s41583-018-0067-3. URL: <http://www.nature.com/articles/s41583-018-0067-3> (visited on 10/12/2022).
 - [10] Reisa A. Sperling et al. “Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease”. In: *Alzheimer’s & Dementia* 7.3 (May 2011), pp. 280–292. ISSN: 1552-5260, 1552-5279. DOI: 10.1016/j.jalz.2011.03.003. URL: <https://onlinelibrary.wiley.com/doi/10.1016/j.jalz.2011.03.003> (visited on 10/30/2022).
 - [11] Guo-fang Chen et al. “Amyloid beta: structure, biology and structure-based therapeutic development”. en. In: *Acta Pharmacologica Sinica* 38.9 (Sept. 2017), pp. 1205–1235. ISSN: 1671-4083, 1745-7254. DOI: 10.1038/aps.2017.28. URL: <https://www.nature.com/articles/aps201728> (visited on 08/09/2023).
 - [12] Denisa Floriana Vasilica Pîr, Ionica Pirici, and Valerica Tudoric. “Tau protein in neurodegenerative diseases – a review”. In: ().
 - [13] Qiuting Wen et al. “White matter alterations in early-stage Alzheimer’s disease: A tract-specific study”. en. In: *Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring* 11.1 (Dec. 2019), pp. 576–587. ISSN: 2352-8729, 2352-8729. DOI: 10.1016/j.dadm.2019.06.003. URL: <https://onlinelibrary.wiley.com/doi/abs/10.1016/j.dadm.2019.06.003> (visited on 08/15/2023).
 - [14] Chantel D. Mayo et al. “Longitudinal changes in microstructural white matter metrics in Alzheimer’s disease”. In: *NeuroImage: Clinical* 13 (2017), pp. 330–338. ISSN: 22131582. DOI: 10.1016/j.nicl.2016.12.012. URL: <https://linkinghub.elsevier.com/retrieve/pii/S2213158216302492> (visited on 10/12/2022).
 - [15] Saori Fujie et al. “The Role of the Uncinate Fasciculus in Memory and Emotional Recognition in Amnesic Mild Cognitive Impairment”. en. In: *Dementia and Geriatric Cognitive Disorders* 26.5 (2008), pp. 432–439. ISSN: 1420-8008, 1421-9824. DOI: 10.1159/000165381. URL: <https://www.karger.com/Article/FullText/165381> (visited on 08/15/2023).

-
- [16] Xiuwei Fu et al. “Microstructural White Matter Alterations in Mild Cognitive Impairment and Alzheimer’s Disease: Study Based on Neurite Orientation Dispersion and Density Imaging (NODDI)”. en. In: *Clinical Neuroradiology* 30.3 (Sept. 2020), pp. 569–579. ISSN: 1869-1439, 1869-1447. DOI: 10.1007/s00062-019-00805-0. URL: <http://link.springer.com/10.1007/s00062-019-00805-0> (visited on 08/15/2023).
 - [17] Catherine F. Slattery et al. “ApoE influences regional white-matter axonal density loss in Alzheimer’s disease”. en. In: *Neurobiology of Aging* 57 (Sept. 2017), pp. 8–17. ISSN: 01974580. DOI: 10.1016/j.neurobiolaging.2017.04.021. URL: <https://linkinghub.elsevier.com/retrieve/pii/S0197458017301495> (visited on 08/14/2023).
 - [18] N. Colgan et al. “Application of neurite orientation dispersion and density imaging (NODDI) to a tau pathology model of Alzheimer’s disease”. en. In: *NeuroImage* 125 (Jan. 2016), pp. 739–744. ISSN: 10538119. DOI: 10.1016/j.neuroimage.2015.10.043. URL: <https://linkinghub.elsevier.com/retrieve/pii/S1053811915009544> (visited on 08/14/2023).
 - [19] Karl Herholz et al. “Metabolic regional and network changes in Alzheimer’s disease subtypes”. en. In: *Journal of Cerebral Blood Flow & Metabolism* 38.10 (Oct. 2018), pp. 1796–1806. ISSN: 0271-678X, 1559-7016. DOI: 10.1177/0271678X17718436. URL: <http://journals.sagepub.com/doi/10.1177/0271678X17718436> (visited on 08/15/2023).
 - [20] for the Alzheimer’s Disease Neuroimaging Initiative, Stefan Teipel, and Michel J. Grothe. “Does posterior cingulate hypometabolism result from disconnection or local pathology across preclinical and clinical stages of Alzheimer’s disease?” en. In: *European Journal of Nuclear Medicine and Molecular Imaging* 43.3 (Mar. 2016), pp. 526–536. ISSN: 1619-7070, 1619-7089. DOI: 10.1007/s00259-015-3222-3. URL: <http://link.springer.com/10.1007/s00259-015-3222-3> (visited on 08/15/2023).
 - [21] Heidi I. L. Jacobs et al. “Structural tract alterations predict downstream tau accumulation in amyloid-positive older individuals”. In: *Nature Neuroscience* 21.3 (Mar. 2018), pp. 424–431. ISSN: 1097-6256, 1546-1726. DOI: 10.1038/s41593-018-0070-z. URL: <http://www.nature.com/articles/s41593-018-0070-z> (visited on 10/30/2022).
 - [22] *Current Edition*. en. URL: <https://www.dicomstandard.org/current> (visited on 08/14/2023).
 - [23] dfwg. *NIfTI: — Neuroimaging Informatics Technology Initiative*. en. Document. URL: <https://nifti.nimh.nih.gov/> (visited on 08/14/2023).

-
- [24] *dcm2niix*. URL: <https://github.com/rordenlab/dcm2niix> (visited on 05/06/2023).
 - [25] Colin Vanden Bulcke et al. “BMAT: An open-source BIDS managing and analysis tool”. en. In: *NeuroImage: Clinical* 36 (2022), p. 103252. ISSN: 22131582. DOI: 10.1016/j.nicl.2022.103252. URL: <https://linkinghub.elsevier.com/retrieve/pii/S2213158222003175> (visited on 08/14/2023).
 - [26] *Introduction to ElikoPy — ElikoPy documentation*. URL: <https://elikopy.readthedocs.io/en/latest/introduction.html> (visited on 08/14/2023).
 - [27] Eleftherios Garyfallidis et al. “Dipy, a library for the analysis of diffusion MRI data”. In: *Frontiers in Neuroinformatics* 8 (Feb. 2014). ISSN: 1662-5196. DOI: 10.3389/fninf.2014.00008. URL: <http://journal.frontiersin.org/article/10.3389/fninf.2014.00008/abstract> (visited on 08/14/2023).
 - [28] Rutger H. J. Fick, Demian Wassermann, and Rachid Deriche. “The Dmipy Toolbox: Diffusion MRI Multi-Compartment Modeling and Microstructure Recovery Made Easy”. In: *Frontiers in Neuroinformatics* 13 (Oct. 2019), p. 64. ISSN: 1662-5196. DOI: 10.3389/fninf.2019.00064. URL: <https://www.frontiersin.org/article/10.3389/fninf.2019.00064/full> (visited on 08/14/2023).
 - [29] *Preprocessing of diffusion images — ElikoPy documentation*. URL: https://elikopy.readthedocs.io/en/latest/preprocessing_dmri.html (visited on 08/09/2023).
 - [30] Rahul S. Desikan et al. “An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest”. en. In: *NeuroImage* 31.3 (July 2006), pp. 968–980. ISSN: 10538119. DOI: 10.1016/j.neuroimage.2006.01.021. URL: <https://linkinghub.elsevier.com/retrieve/pii/S1053811906000437> (visited on 08/14/2023).
 - [31] URL: <https://github.com/miykael/atlasreader/tree/master/atlasreader/data> (visited on 05/06/2023).
 - [32] URL: <https://www.natbrainlab.co.uk/atlas-maps> (visited on 05/06/2023).
 - [33] Marco Catani and Michel Thiebaut de Schotten. “A diffusion tensor imaging tractography atlas for virtual in vivo dissections”. eng. In: *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 44.8 (Sept. 2008), pp. 1105–1132. ISSN: 0010-9452. DOI: 10.1016/j.cortex.2008.05.004.
 - [34] Shaun Warrington et al. “XTRACT - Standardised protocols for automated tractography in the human and macaque brain”. In: *Neuroimage* 217 (Aug. 2020), p. 116923. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2020.116923. URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260058/> (visited on 05/28/2023).

-
- [35] Matthew F. Glasser et al. “The minimal preprocessing pipelines for the Human Connectome Project”. eng. In: *NeuroImage* 80 (Oct. 2013), pp. 105–124. ISSN: 1095-9572. DOI: 10.1016/j.neuroimage.2013.04.127.
- [36] Ben Jeurissen et al. “Diffusion MRI fiber tractography of the brain”. en. In: *NMR in Biomedicine* 32.4 (Apr. 2019). ISSN: 0952-3480, 1099-1492. DOI: 10.1002/nbm.3785. URL: <https://onlinelibrary.wiley.com/doi/10.1002/nbm.3785> (visited on 08/09/2023).
- [37] *TrackVis*. URL: <http://trackvis.org/> (visited on 08/18/2023).
- [38] *statsmodels/statsmodels: Release 0.14.0*. May 2023. DOI: 10.5281/ZENODO.593847. URL: <https://zenodo.org/record/593847> (visited on 08/18/2023).
- [39] Michael Waskom. “seaborn: statistical data visualization”. In: *Journal of Open Source Software* 6.60 (Apr. 2021), p. 3021. ISSN: 2475-9066. DOI: 10.21105/joss.03021. URL: <https://joss.theoj.org/papers/10.21105/joss.03021> (visited on 08/18/2023).
- [40] Marc Teichmann et al. “Free and Cued Selective Reminding Test – accuracy for the differential diagnosis of Alzheimer’s and neurodegenerative diseases: A large-scale biomarker-characterized monocenter cohort study (ClinAD)”. en. In: *Alzheimer’s & Dementia* 13.8 (Aug. 2017), pp. 913–923. ISSN: 1552-5260, 1552-5279. DOI: 10.1016/j.jalz.2016.12.014. URL: <https://onlinelibrary.wiley.com/doi/10.1016/j.jalz.2016.12.014> (visited on 08/09/2023).
- [41] Béatrice Desgranges et al. “The Neural Basis of Intrusions in Free Recall and Cued Recall: A PET Study in Alzheimer’s Disease”. en. In: *NeuroImage* 17.3 (Nov. 2002), pp. 1658–1664. ISSN: 10538119. DOI: 10.1006/nimg.2002.1289. URL: <https://linkinghub.elsevier.com/retrieve/pii/S1053811902912899> (visited on 08/12/2023).
- [42] Nienke M.E. Scheltens et al. “Hypometabolism of the posterior cingulate cortex is not restricted to Alzheimer’s disease”. en. In: *NeuroImage: Clinical* 19 (2018), pp. 625–632. ISSN: 22131582. DOI: 10.1016/j.nicl.2018.05.024. URL: <https://linkinghub.elsevier.com/retrieve/pii/S2213158218301700> (visited on 08/16/2023).
- [43] *NITRC: MRICroGL: Tool/Resource Info*. URL: <https://www.nitrc.org/projects/mricrogl/> (visited on 08/16/2023).

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