

École polytechnique de Louvain

Multimodal investigation of Tau accumulation and functional connectivity in Alzheimer's disease

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Abstract

Alzheimer’s disease is associated with a progressive accumulation of tau protein and global alterations in large-scale functional brain networks. In recent years, there has been growing interest in how these processes relate to each other, especially in the early stages of the disease. Even though numerous studies have examined tau protein accumulation and functional connectivity, the relationship is still not fully understood.

The aim of this research is to establish the association between regional tau aggregation and functional brain connectivity using a multimodal approach, involving the application of both positron emission tomography (PET) and resting-state functional magnetic resonance imaging (rs-fMRI). To assess functional connectivity, lagged cross-correlation analysis was applied to examine the temporal association between regional Blood Oxygen Level Dependent (BOLD) signals, and graph theoretical measures were further used to characterise the functional connectivity.

These results suggest an increasing tau deposition across clinical stages, with a clear involvement of areas commonly involved in the early phase of Alzheimer’s disease. Functional connectivity showed non-linear trends among clinical stages with initial increases in connectivity within intermediate stages followed by decreases in later stages. Importantly, a significant spatial association was found between functional connectivity and inter-regional tau similarity patterns, suggesting that tau pathology progression might follow functional brain networks.

These results are consistent with the network-based transmission theory of tau pathology, emphasising the importance of taking into account the large-scale structure of the brain in Alzheimer’s disease. This research enhances our knowledge regarding the underlying disease mechanisms and supports the creation of early biomarkers by combining multiple imaging modalities.

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Abbreviations

A β Amyloid-beta.

AD Alzheimer's disease.

APOE Apolipoprotein E.

APP Amyloid Precursor Protein.

BOLD Blood Oxygen Level Dependent.

CN Cognitively Normal.

CSF Cerebrospinal Fluid.

DEM dementia.

dFC Dynamic Functional Connectivity.

DMN Default Mode Network.

DVARS Derivative of RMS Variance over voxels.

E_g Global Efficiency.

E_l Local Efficiency.

EPI Echo-Planar Imaging.

ESM Epidemic Spread Model.

FC Functional Connectivity.

FCSRT Free and Cued Selective Reminding Test.

FDG-PET Fluorodeoxyglucose Positron Emission Tomography.

FDR False Discovery Rate.

fMRI functional magnetic resonance imaging.

FOV Field of View.

GSR Global Signal Regression.

ICA Independent Component Analysis.

LTD Long-Term Depression.

LTP Long-Term Potentiation.

MCA Manifold Component Analysis.

MCI Mild Cognitive Impairment.

MMSE Mini-Mental State Examination.

MRI Magnetic Resonance Imaging.

MTL Medial Temporal Lobe.

NFT Neurofibrillary Tangle.

PART Primary Age-Related Tauopathy.

PCA Posterior Cortical Atrophy.

PCC Posterior Cingulate Cortex.

PET Positron Emission Tomography.

PNA Progressive Non-fluent Aphasia.

PSF Point Spread Function.

ROI Region of Interest.

rs-fMRI resting-state functional magnetic resonance imaging.

RSN Resting-State Network.

SCA Seed-based Cross-correlation Analysis.

SUVr Standardised Uptake Value ratio.

TE Echo Time.

TMT Trail Making Test.

TR Repetition Time.

Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. With ageing populations across the world, its prevalence is expected to increase substantially in the coming years, making it one of the major public health challenges of the current era [1]. From a clinical perspective, AD is associated with a gradual decline in cognitive ability, including episodic memory, executive function, language, and visuospatial skills [2, 3].

Biologically speaking, AD is characterised by the presence of two pathological proteins in the brain: extracellular Amyloid-beta ($A\beta$) plaques and intracellular tau Neurofibrillary Tangles (NFTs) [4, 5]. Although amyloid aggregation is thought to mark the early stages of the disease process [3], increasing evidence suggests that the involvement of tau is more directly associated with neurodegeneration and cognitive impairment [6, 7]. The build-up of tau protein displays a pattern that is relatively well understood, beginning in the transentorhinal and entorhinal cortex, followed by subsequent propagation to the limbic system, the associative neocortex, and eventually the primary cortex, a pattern captured by the Braak staging criteria [8, 9]. Importantly, this spread is not seen to be dependent on the simple adjacency of brain structures but on their connectivity, implying that tau spreads trans-synaptically along functional pathways rather than simply diffusing within the brain tissue [10, 11].

Concurrently, developments in neuroimaging techniques have made the study of the organisation of large-scale brain networks within living brains possible. Resting-state functional magnetic resonance imaging (rs-fMRI) allows for the examination of Functional Connectivity (FC), which is the correlation in time of Blood Oxygen Level Dependent (BOLD) signal fluctuations across spatially separated brain regions, without any invasive procedure [12, 13]. The disruption of functional brain networks such as the Default Mode Network (DMN), salience network, and frontoparietal control network is seen in patients with AD [14–16]. FC can be studied either through a static approach, as a single average measure across the full scan, or through a dynamic approach. Dynamic connectivity in the present study was assessed using Seed-based Cross-correlation Analysis (SCA) because this approach takes into account the temporal

nature of the interaction process between regions rather than state-based measures [17, 18]. Additional analyses with graph theory measures were also computed in order to further characterise functional network organisation [19].

While these developments are significant, there is still an incomplete understanding of the connection between tauopathy and brain network function. Although considerable research has examined both processes [11, 20, 21], comparatively little work has attempted to correlate tau distribution with brain network functioning throughout the entire disease course. In particular, the extent to which tau pathology is associated with the underlying functional brain networks rather than structural connections or anatomic proximity still lacks systematic quantification across multiple methods including tau Positron Emission Tomography (PET) imaging, rs-fMRI, and graph theory.

The aim of this study is to examine the relationship between regional tau deposition and brain functional connectivity by using multiple imaging techniques such as tau PET with [18F]MK-6240 and rs-fMRI among a large number of participants across the AD clinical spectrum, including 220 patients who underwent tau PET imaging and 161 patients who underwent rs-fMRI scans, of whom 111 had matched multimodal acquisitions available for combined analyses.

Specifically, the goals of the current study include (i) defining the pattern of regional tau accumulation and its progression through different clinical stages; (ii) assessing whether the tau burden accumulation is biased toward certain network characteristics, such as degree and clustering; (iii) describing the changes in functional network topology across different clinical groups based on graph theoretical measures; (iv) directly assessing the relationship between tau burden and FC both locally and globally; (v) testing whether there is a similarity between the spatial pattern of tau pathology and functional brain networks via pairwise and seed-based analysis; and (vi) analysing the tau burden accumulation over time via longitudinal PET imaging. Ultimately, this master's thesis aims to improve the understanding of AD as a network-based disease and support the development of early biomarkers through the integration of various brain imaging data modalities.

Part I

Theoretical background

Chapter 1

Biological and clinical background

1.1 Pathophysiology of Alzheimer's disease

1.1.1 Classical amyloid cascade model

AD is a progressive neurodegenerative disorder defined by the accumulation of two major pathological proteins in the brain: $A\beta$ and tau. Under physiological conditions, tau is a microtubule-associated protein that contributes to the stabilisation of the neuronal cytoskeleton and supports axonal transport. The Amyloid Precursor Protein (APP), from which $A\beta$ peptides are derived, is involved in several neuronal processes including synaptic function and cellular signalling.

However, in AD, these two proteins are pathologically altered. An abnormal cleavage of APP induces the build-up and aggregation of extracellular $A\beta$ plaques, while tau protein undergoes hyperphosphorylation, dissociates from microtubules and gradually aggregates to form intracellular NFTs. Both lesions constitute the principal neuropathological features of AD, with their accumulation being closely linked to neurodegeneration, synaptic dysfunction, and cognitive decline [5, 22].

For several decades, the prevailing pathophysiological model proposed that the accumulation of $A\beta$ represented the initiating event in AD, triggering downstream tau pathology and ultimately leading to neurodegeneration. According to this classical amyloid cascade hypothesis, $A\beta$ was considered the primary driver of the disease, while tau pathology was viewed mainly as a secondary downstream consequence of $A\beta$ accumulation. The interaction between $A\beta$ and tau was therefore initially considered largely unidirectional [22].

However, recent research, in both human studies and animal models, challenges this traditional model. These studies show that $A\beta$ and tau interact directly and synergisti-

cally, thereby amplifying neuronal dysfunction and accelerating the progression of the disease [22].

From a temporal perspective, the accumulation of $A\beta$ plaques begins in the very early stages of the disease, often 10 to 20 years before the first clinical symptoms appear, while tau aggregates appear later, and progressively spread across the brain. Therefore, $A\beta$ is associated with an early-stage phenomenon, whereas tau is more directly correlated with clinical symptoms, neurodegeneration, cerebral atrophy and cognitive decline [23].

Nevertheless, the amyloid cascade model has several limitations. Although reducing $A\beta$ has shown promising results in animal models, these findings have not led to a significant improvement in cognitive function or a slowing of disease progression in humans. This observation could be explained by the fact that animal models often exhibit isolated $A\beta$ pathology, while in human patients, $A\beta$ coexists with tau and neurodegeneration. This emphasises the importance of $A\beta$ and tau interaction for a better understanding of the disease's pathophysiology [22].

1.1.2 $A\beta$ -tau interactions and network dysfunction

Recent data indicate a dynamic, bidirectional interaction between $A\beta$ and tau. Not only does $A\beta$ induce tau pathology, but tau also seems to modulate the effects of $A\beta$, creating a vicious cycle that amplifies neuronal damage [22].

At the cellular level, $A\beta$ and tau contribute to widespread neuronal dysfunction through multiple mechanisms involving mitochondrial impairment, synaptic alterations, and dysregulation of intracellular pathways [22]. At the mechanistic level, $A\beta$ is associated with neuronal hyperactivity, especially in dystrophic neurites and regions containing plaques, even in the absence of tau overexpression. $A\beta$ also promotes tau hyperphosphorylation and accelerates its spread throughout the brain. In the presence of $A\beta$, the spread of tau extends beyond the entorhinal cortex, but remains limited in the absence of $A\beta$ [15, 22]. Amyloid plaques create a pathological microenvironment with neuronal hyperactivity and glial activation [24], thereby encouraging tau aggregation and spread throughout the brain networks (see Figure 1.1).

The spread of tau follows connected neural networks, implying a trans-synaptic transmission mechanism that depends on the architecture of brain networks. This network organisation is a central part of understanding the changes in FC observed in AD. Moreover, $A\beta$ is directly linked to functional brain connectivity. It has been shown that $A\beta$ is closely linked to alterations in the DMN, mainly in the Posterior Cingulate Cortex (PCC), a region connected to the hippocampus via the cingulum. The accumulation of $A\beta$ in these regions correlates with cortical hypometabolism, episodic memory deficits and impaired hippocampal connections, observed very early in the disease [22].

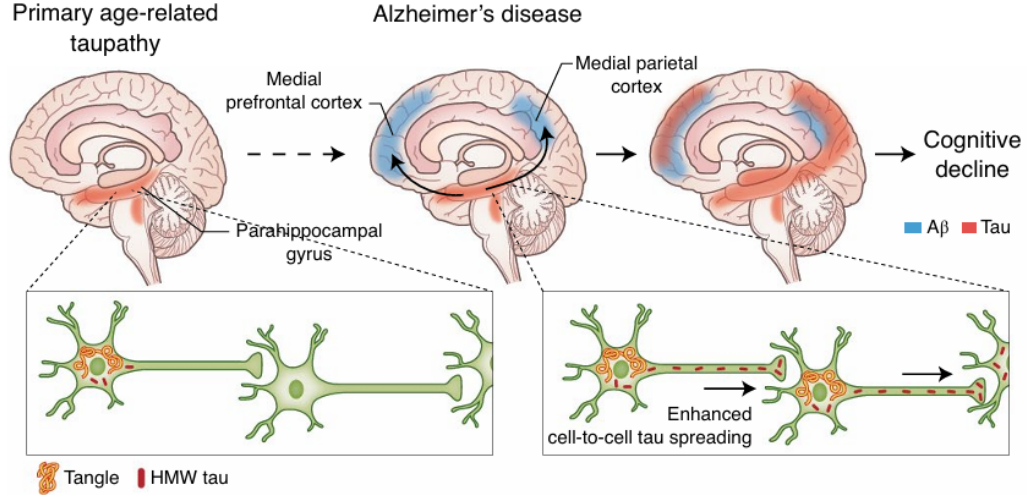


Figure 1.1: *Illustration of synergy between $A\beta$ and tau in AD. Presence of $A\beta$ facilitates the aggregation and spread of pathological high molecular weight (HMW) of tau, leading to NFT formation and spreading of tau pathology throughout connected areas of the brain, resulting in cognitive impairment. Adapted from [22].*

In the context of synapses, the pathological changes in tau affect neural signalling and neurotransmitter secretion, mainly because of the abnormal intracellular location of the protein. In addition, $A\beta$ and tau can influence synaptic plasticity by affecting the mechanisms responsible for Long-Term Potentiation (LTP) and Long-Term Depression (LTD) processes, important for learning and memory. Such alterations result in an ongoing loss of synapses that is highly associated with the cognitive impairment typical of AD.

While $A\beta$ induces neuronal hyperactivity, tau tends to inhibit it [15]. Their interaction generates a complex dynamic characterised by initial neuronal hyperactivity, then dysfunction and hypoactivity, leading to a desynchronisation of neuronal networks and abnormal oscillations (see Figure 1.2).

A central mechanism behind this toxicity is calcium (Ca^{2+}) dysregulation. $A\beta$ disrupts calcium channels, particularly NMDA and voltage-gated channels, leading to an increase in intracellular Ca^{2+} . This activates intracellular cascades, including the phosphorylation of tau via GSK3 β , thereby causing dysregulation of gene expression and neuronal dysfunction. Tau reduction helps to decrease neuronal hyperexcitability and synaptic dysfunction, and helps mediate the toxic effects of $A\beta$ [22].

Lastly, microglia, which are glial cells within the central nervous system, are key players in the $A\beta$ -tau interaction. The activation of these cells, stimulated by both $A\beta$ and tau, results in the release of inflammatory cytokines that contribute to the propagation of tau. In essence, microglia have a dual function, initially being beneficial through the phagocytosis of $A\beta$, but later becoming damaging by causing chronic inflammation and

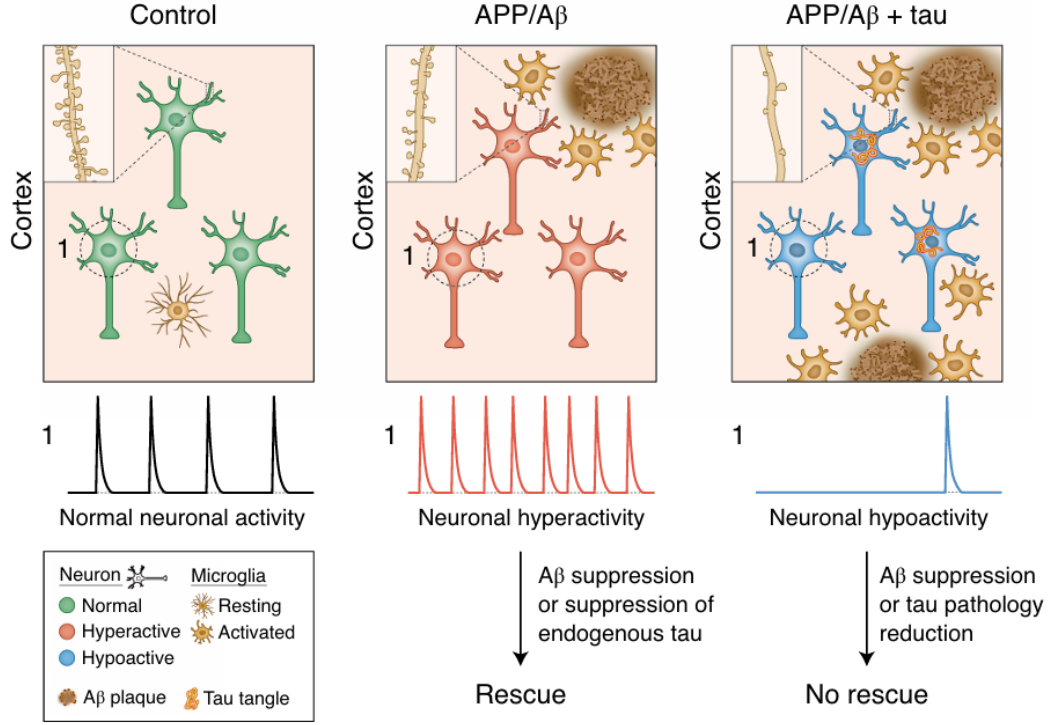


Figure 1.2: Illustration of the synergistic role of protein/Aβ (APP/Aβ) and tau pathologies on neuronal excitability and synapse dysfunction. In comparison with the control situation, the presence of APP/Aβ leads to increased neuronal excitability. The downregulation of Aβ or the reduction of tau gene expression restores normal neuronal excitability ("rescue"). But in the case of preexisting tau pathology, neuronal hypoactivity occurs, where Aβ downregulation does not result in neuronal rescue ("no rescue").

tau propagation [22].

AD thus involves a complex and dynamic interaction between Aβ and tau, leading to alterations in neuronal activity, synaptic plasticity and brain networks, and providing the basis for the cognitive deficits observed in patients. It can therefore no longer be described as a simple linear cascade, but rather as a dynamic process involving all these interactions.

1.2 Clinical stages of Alzheimer's disease

1.2.1 Clinical continuum and biomarker-based classification

AD is now considered a biological continuum extending from early biological changes to clinical dementia (DEM) [2]. These pathological changes may begin years before the onset of symptoms. Clinically, the disease can progress from a preclinical stage to Mild Cognitive Impairment (MCI), and eventually to DEM. MCI represents an intermediate stage, characterised by measurable cognitive decline without major loss of

independence, whereas DEM involves cognitive impairment severe enough to interfere with daily functioning [2].

Current diagnostic guidelines include clinical measures as well as biochemical markers that show evidence of amyloid deposits, tau pathology, and neurodegeneration [2]. These markers include PET scanning, Cerebrospinal Fluid (CSF) markers, Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) hypometabolism, and atrophy markers on Magnetic Resonance Imaging (MRI) scans. This method allows for biological classification of AD and is helpful in enhancing the accuracy of diagnosis especially in scientific studies. People showing signs of amyloid deposits are usually described as $A\beta$ positive ($A\beta+$) while people lacking amyloid deposits are $A\beta$ negative ($A\beta-$).

1.2.2 Preclinical stages of Alzheimer's disease

In addition to this classification, research by the NIA-AA¹ has introduced the concept of a preclinical stage of AD. This stage is defined by the absence of clinical symptoms despite the presence of early biological changes, such as $A\beta$ accumulation, often several years or even decades before the onset of DEM [3].

The course of the disease can thus be said to follow a continuum from the normal state to the preclinical state, then on to MCI, and ultimately ending in DEM. As can be seen in Figure 1.3, this process is not always a linear one; biological processes and clinical manifestations evolve in parallel but along distinct trajectories, which suggests that there is some temporal dissociation between the pathology and symptoms.

The proposed biomarker model is based on a typical sequence of events: early accumulation of $A\beta$, followed by tau pathology and neurodegeneration, and finally the appearance of clinical symptoms [3].

It is clear from these observations that there is a need for studying the preclinical phase of AD and looking out for biomarkers before cognitive impairment starts.

1.2.3 Variability and implications of disease staging

The progression of the disease varies significantly from person to person and is influenced by genetic factors such as the Apolipoprotein E (APOE) gene, environmental factors, comorbidities, and cognitive reserve [1, 3]. Some individuals may cope with the disease for longer thanks to compensatory mechanisms, making it difficult to establish uniform models of progression.

This inter-individual variability complicates the identification of reliable early biomarkers and highlights the importance of studying the preclinical stages of AD.

¹National Institute on Aging and Alzheimer's Association.

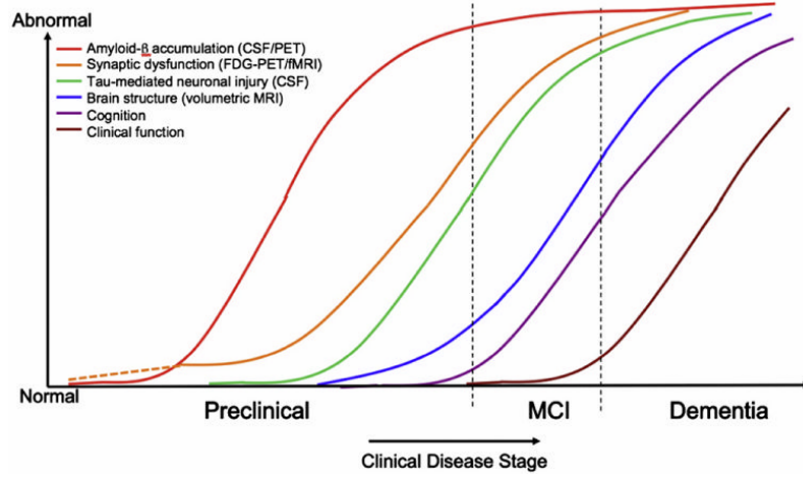


Figure 1.3: *Hypothetical model for biomarkers of AD dynamics applied to understand the preclinical period. Adapted from [3]*

1.3 The neuropathology of Alzheimer’s disease

Tau tangles follow a typical pattern of progression, beginning in the transentorhinal region, then spreading to the limbic system, particularly the hippocampus, to the associative neocortex, and finally to broader cortical regions, according to Braak’s staging system (see Figure 1.4). This progression is directly correlated with clinical severity and the extent of cognitive symptoms. A ‘prion-like’ trans-synaptic diffusion mechanism has been proposed to explain this spread, involving transmission along neuronal connections [5].

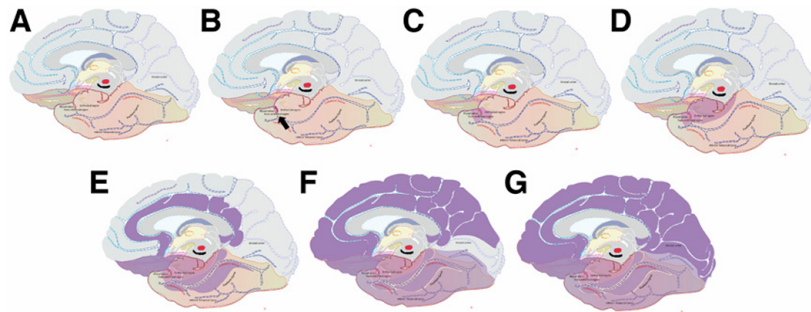


Figure 1.4: *Topographic map showing the Braak staging from 0 to VI, demonstrating how the spatial progression of the pathologic changes in tau protein occur with reference to the initial staging criteria. The areas involved in the brain are marked in purple to show the gradual involvement of areas from the transentorhinal stage to the neocortex. Adapted from [9].*

In contrast to tau pathology, $A\beta$ accumulation is more diffusely distributed throughout the brain and does not follow the same stereotypical progression pattern [5].

Neuropathological staging systems, such as the ABC score, combine amyloid deposition, tau pathology according to Braak staging, and neuritic plaque burden to assess the

severity of AD neuropathological changes (see Appendix B.1) [4].

However, AD is rarely isolated but frequently coexists with other brain disorders, such as vascular diseases, Lewy body DEM, TDP-43 DEM, and Primary Age-Related Tauopathy (PART). This complicates diagnosis and may influence the clinical presentation of symptoms. Due to this pathological overlap, the exact contribution of each condition to cognitive decline is difficult to determine [5]. Moreover, there is no clear standard for quantifying Alzheimer’s pathology relative to other pathologies, contributing to a wide variability in the clinical presentation of the disease [5]. Certain regions, particularly the hippocampus and temporal cortex, appear especially vulnerable to AD pathology. Other cases may present atypical forms of AD, characterised by relatively preserved memory function and deficits in vision, language, executive function, or behaviour.

Despite considerable progress in understanding AD neuropathology, important limitations remain in explaining the heterogeneous relationships between pathology and clinical symptoms, reflecting the substantial inter-individual variability of the disease [5]. Overall, AD neuropathology is characterised by the progressive accumulation and propagation of $A\beta$ plaques and tau tangles. While $A\beta$ is a good predictor of future cognitive decline, tau pathology shows a stronger cross-sectional association with clinical function than $A\beta$. Nevertheless, mixed pathologies and inter-individual variability continue to complicate the understanding, diagnosis, and treatment of the disease.

Chapter 2

Imaging in Alzheimer's disease

2.1 Tau PET

PET is an advanced molecular imaging technique that uses a radioactive tracer to visualise molecular processes in the brain in vivo [25]. The tracer binds specifically to a target molecule, thereby enabling its distribution within the brain to be mapped. This technique is useful for detecting the accumulation of pathological proteins, such as those associated with tauopathies. In the context of AD, tau PET imaging relies on the use of specific ligands that bind to pathological tau aggregates, specifically NFTs, for in vivo visualisation and quantification of tau pathology. Before the introduction of this technology, the measurement of tau was limited to analysis of CSF or post-mortem autopsy [6, 23].

There have been several tau PET tracers introduced that can identify tau protein aggregates pathologically. One such tracer that belongs to the first generation is ^{18}F -AV-1451, also known as flortaucipir. This tracer was extensively used during the early stages of tau imaging [6]. Nevertheless, there were some limitations with these tracers, including non-specific off-target binding [23]. Therefore, researchers decided to design new specific and sensitive radiotracers belonging to the second generation, like MK-6240 [23].

Tau PET imaging makes it possible to create a spatial map of tau distribution in the brain and to observe its progression over time. Studies have shown that tau accumulation follows specific anatomical patterns, broadly corresponding, as previously mentioned, to Braak's neuropathological classification (see Figure 2.1) [6, 23]. In Cognitively Normal (CN) older adults, tau deposition is mainly observed in the Medial Temporal Lobe (MTL). But in patients with AD, tau pathology spreads progressively to neocortical regions, such as the temporal and parietal lobes. Patients with AD also show high

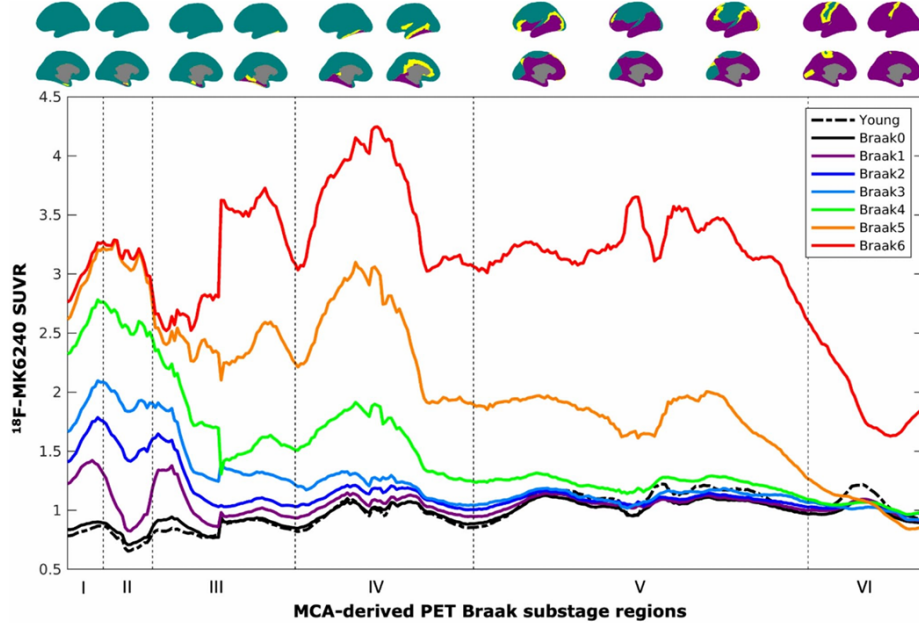


Figure 2.1: *Manifold Component Analysis (MCA)-derived PET Braak substage signatures show the extent of tau deposition according to the region of Braak staging by means of ^{18}F -MK6240 PET Standardised Uptake Value ratio (SUVR)s. These curves provide the average intensity of tau deposition in PET Braak substages according to different stages of Braak staging. The illustrations of brain sections shown above the graph demonstrate the locations of tau pathology in relation to Braak stages, where magenta represents previous stages and yellow represents the current stage. Adapted from [26].*

levels of tau tracer binding compared with control subjects, and this tau load is strongly correlated with neurodegeneration and cognitive decline, supporting the role of tau in the clinical progression of the disease [6, 23].

Despite the considerable advances made possible by tau PET imaging, challenges remain regarding tracer specificity and PET signal quantification. Quantification may be influenced by inter-individual differences in tracer uptake and imaging-related artefacts, while the identification of tau pathology relative to other proteinopathies and comorbid conditions remains difficult [23].

2.2 Resting-state fMRI (rs-fMRI)

2.2.1 Principles of rs-fMRI and BOLD signal

rs-fMRI was introduced by Biswal et al. in 1995 [12] and has since become an indispensable neuroimaging technique for studying the brain's FC. This technique is based on the analysis of the BOLD signal, discovered by Ogawa et al. in the early 1990s [13]. The BOLD signal reflects variations in the concentration of deoxyhemoglobin in cerebral blood vessels resulting from neurovascular coupling mechanisms. Increased neuronal

activity induces a local increase in cerebral blood flow and oxygen delivery that exceeds oxygen consumption, thereby decreasing local deoxyhemoglobin concentration and modifying magnetic resonance signal intensity. Since deoxyhemoglobin is paramagnetic, these changes generate detectable variations in the MRI signal, which are indirectly associated with neuronal activity. rs-fMRI measures spontaneous fluctuations in the BOLD signal at low frequencies (<0.1 Hz) observed in the absence of an explicit task. This enables the study of brain activity at rest, providing a better understanding of the functional architecture of brain networks [27, 28].

2.2.2 Resting-State Networks (RSNs) and FC

FC analysis based on BOLD signal fluctuations allows the identification of temporal correlations between different brain regions. This approach has identified several RSNs, characterised by synchronisation of the BOLD signal between spatially distinct regions. Among the most studied RSNs is the DMN, mainly involved in internally directed cognitive processes such as autobiographical memory and self-referential thinking. Other important networks include the salience network, implicated in the detection of salient stimuli and network switching, the sensorimotor network, the visual network, and attentional networks involved in executive and cognitive control processes.

These functional networks demonstrate robust reproducibility and stability among individuals, which makes them ideal targets for the study of neurological and psychiatric disorders [27].

2.2.3 rs-fMRI in Alzheimer’s disease

Over the past two decades, rs-fMRI has seen tremendous growth in neuroscience research. This technique has become a valuable tool to study brain connectivity. For example, AD is one of the conditions that has been the subject of many studies using rs-fMRI. This method can detect early changes in the brain’s FC, even before the clinical symptoms become apparent, which makes it a promising tool for identifying early biomarkers of the disease [27, 28].

One of its major strengths is that it is a non-invasive method that does not require the performance of explicit cognitive tasks, making it suitable for vulnerable populations such as older adults or cognitively impaired patients.

The alterations in FC observed in AD affect networks such as the DMN (see Figure 2.2).

As mentioned earlier, rs-fMRI has many advantages such as its ability to explore brain connectivity without the need for invasive procedures. However, the method also

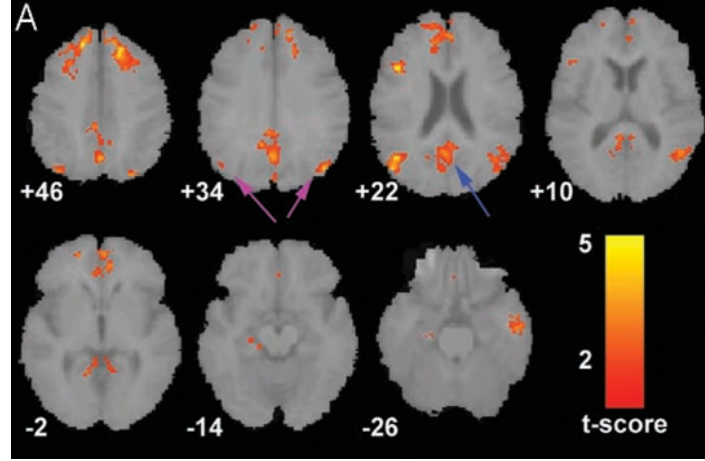


Figure 2.2: *Enhanced level of activity in the DMN of healthy elderly patients. (A) Axial images showing the outcomes from a two-sample t-test that was carried out to compare the DMN of healthy elderly individuals with AD patients. Adapted from [14]*

has certain limitations. For example, individual variations in connectivity patterns might make it more difficult to interpret the results and physiological noise (movement, breathing, etc.), might interfere with the results. Data pre-processing is therefore essential to obtain reliable results.

2.3 Dynamic functional connectivity

Early studies of FC were based on static descriptions of BOLD correlations, presuming that interactions between brain regions remained constant over time. However, studies based on rs-fMRI have shown that FC is not static, but varies dynamically across different time scales depending on cognitive states or in response to external stimuli. Dynamic Functional Connectivity (dFC) therefore aims to study temporal variations in interactions between brain regions, providing a more detailed view of the functional organisation of the brain [17, 18, 29].

2.3.1 Methods for dynamic connectivity analysis

Several approaches are used to analyse these temporal variations in FC. One of the most common is the sliding-window analysis which calculates BOLD signal correlations between brain regions across successive time segments (see Figure 2.3). Some approaches also combine techniques such as Independent Component Analysis (ICA) or clustering methods to identify recurrent patterns of FC across the brain [18]. These analyses have revealed several distinct states of FC that are recurrent and can be interpreted as relatively stable periods of connectivity, separated by transitions between different functional configurations [18].

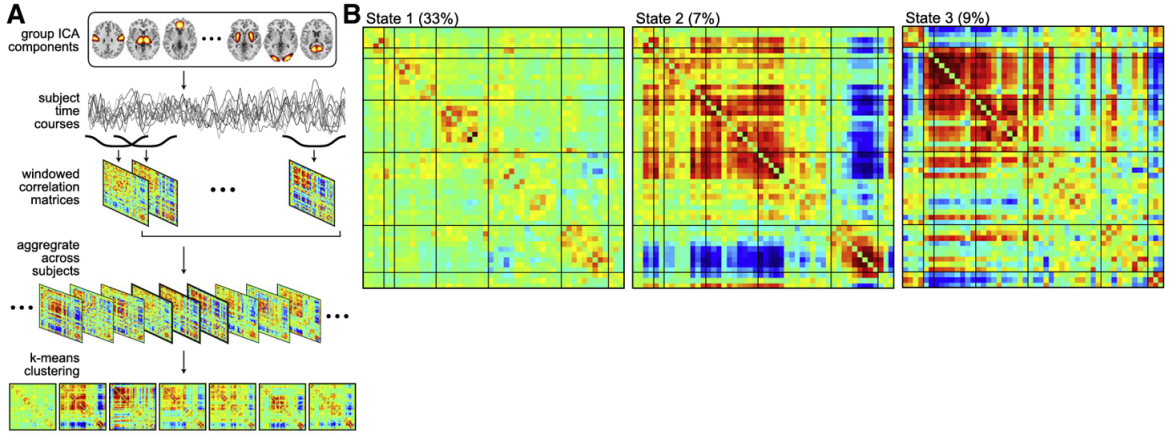


Figure 2.3: *FC states identification using a sliding window/clustering approach.*
Adapted from [17]

However, dynamic connectivity analysis remains methodologically challenging. Results may be influenced by analytical parameters, such as window size in sliding-window approaches, as well as by physiological noise and motion artefacts. Careful preprocessing remains essential to minimise these sources of variability [17].

2.3.2 Network organisation and clinical relevance

Beyond these methodological challenges, connectivity dynamics provide valuable insights into the functional organisation of brain networks. Recent research has shown that functional brain networks are temporally complex but remain organised around a stable hierarchical architecture of correlation patterns. This organisation is based on a backbone of strong, zero-lag connections, alongside weaker connections that are subject to time delays. Although this backbone represents only a small proportion of the network’s connections (around 1–10%), it links a large proportion of the brain’s regions forming the core functional architecture of the network [29].

The study of dynamic connectivity is also of great clinical interest. In fact, several neurological and psychiatric disorders have been linked to alterations in the dynamic properties of brain networks. For example, in AD, alterations in the dynamics of FC have been observed, especially in the DMN. Patients with this condition spend less time in highly connected network states, particularly involving the DMN and more time in less integrated or disrupted connectivity configurations [17]. And even though challenges remain, this approach now represents a promising tool for a better understanding of brain function and functional abnormalities associated with various neurological conditions such as AD [17, 18, 29].

Chapter 3

Link between AD and brain connectivity

3.1 Network-based propagation of tau pathology

Neurofibrillary tangles constitute one of the core pathological features of AD and are characterised by the presence of tau aggregates in the brain, which spread from neuron to neuron via neural connections [11]. In fact, a cross-sectional analysis of tau PET and MRI data has shown that tau accumulation begins in specific regions of the brain, such as the entorhinal cortex, and then gradually spreads to other cortical and subcortical areas. This pattern of spread follows a hierarchical structure, similar to Braak's stages, extending into the associated cortical regions, such as the temporal and parietal lobes.

To simulate this spread, the study by Vogel et al. (2020) [11] used an Epidemic Spread Model (ESM) to predict tau's spread patterns in the human brain (see Figure 3.1).

This model has shown that up to 70% of the observed variation in tau propagation can be explained by functional and anatomical connectivity between brain regions. In $A\beta$ -positive individuals, tau tangles spread more rapidly and to more brain regions compared to $A\beta$ -negative subjects [11]. This progression is influenced by the functional and structural connectivity of brain regions, which explains why certain areas are more vulnerable to tau accumulation depending on their connectivity with other regions affected by the disease [26].

Another approach to better understand tau propagation relies on the use of MCA, a method introduced by Bezgin et al. (2025) [26]. MCA analysis allows tau profiles specific to each individual to be identified, thereby reducing the dilution of information. Unlike the standard approach, MCA analysis captures the spatial continuity of tau progression in regions such as the entorhinal cortex, a primary site of tau accumulation

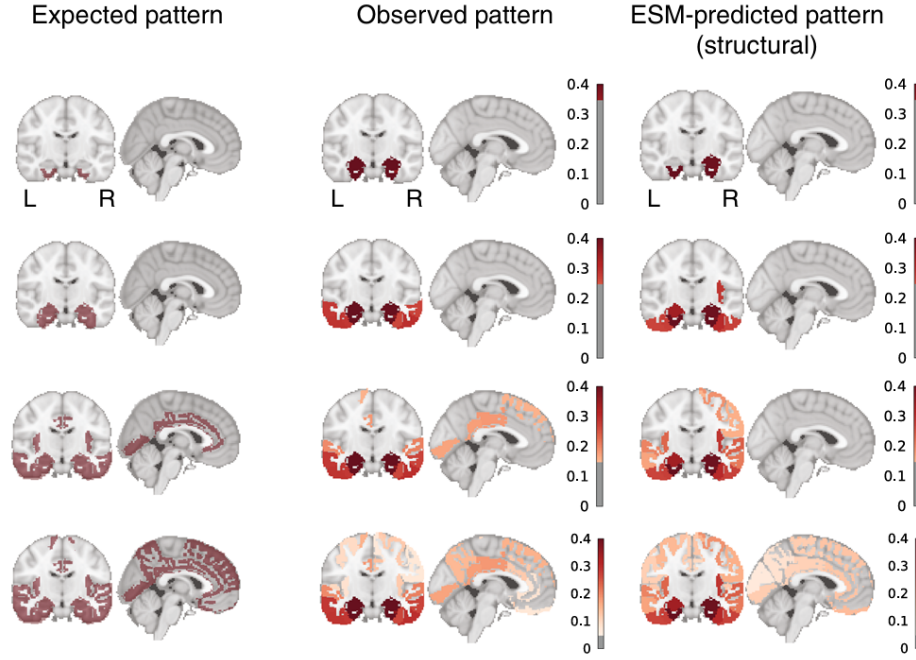


Figure 3.1: Comparison of the hypothesized, observed, and ESM-predicted patterns of spreading of tau pathology. Here, “expected pattern” stands for the hypothesized pattern based on the Braak stages of neuropathology, while “observed pattern” refers to the actual pattern that can be obtained from the tau PET scans. The “ESM-predicted patterns” refer to those simulated using the network of brain structures or functions. Adapted from [11].

[26].

The tau profiles generated by MCA are highly correlated with the results of neuropsychological tests and neuroinflammatory biomarkers, which supports the idea that the accumulation of tau in neural networks has a direct impact on cognition. Its accumulation in specific regions, such as the entorhinal cortex, is associated with measurable cognitive decline.

Overall, connectivity-based models such as ESM and MCA point out the central role of brain networks in tau propagation and have promising clinical applications for evaluating therapeutic interventions and predicting disease progression [11, 26].

3.2 Studies linking PET imaging and FC

In addition to tau PET imaging, amyloid PET imaging enables the in vivo detection of cerebral $A\beta$ deposition. rs-fMRI combined with tau PET and amyloid PET imaging has provided important insights into the combined effects of tau and $A\beta$ on FC [15, 20].

Schultz et al. (2017) [15] demonstrated for instance that the accumulation of these two proteins leads to successive phases of hyperconnectivity, followed by phases of

hypoconnectivity, in specific brain networks such as the DMN and salience networks (see Figure 3.2).

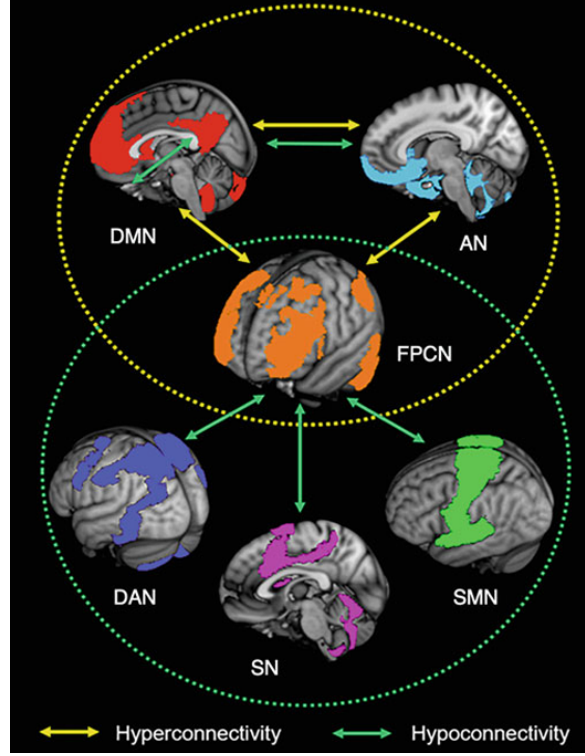


Figure 3.2: Schematic representation of hyperconnectivity and hypoconnectivity occurring within large-scale brain networks at various stages of development of AD in relation to accumulation of tau and $A\beta$. The yellow circles show examples of networks displaying hyperconnectivity in terms of greater FC, such as the DMN, affective network (AN), and frontoparietal network (FPN). Green circles show networks with hypoconnectivity in relation to reduced FC, such as the dorsal attention network (DAN), ventral attention network (VAN), and somatosensory network (SSN). Adapted from [30].

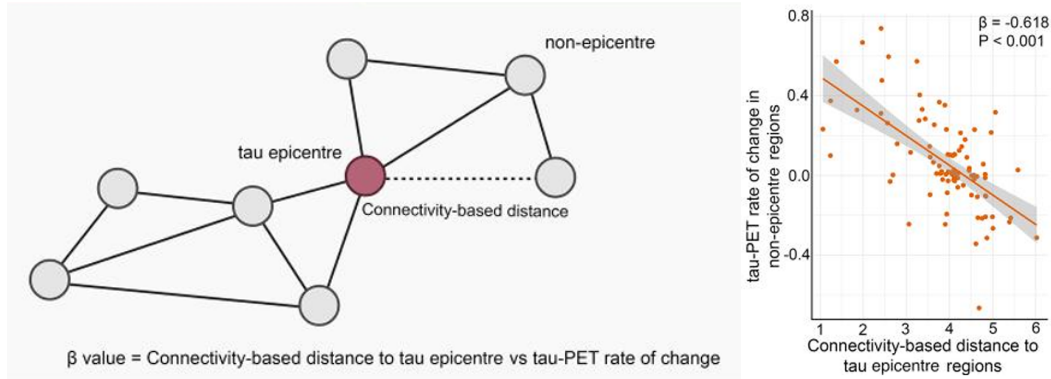
This phenomenon is especially pronounced in regions associated with memory and executive functions, like the entorhinal cortex and the hippocampus. The initial hyperconnectivity is followed by hypoconnectivity in the advanced stages, which may mean that the progression of the disease dynamically affects the FC of brain networks [15].

Studies of functional networks have also revealed that the spread of tau affects connectivity between tau epicentre regions (where tau first accumulates) and non-epicentre regions (where tau later spreads). This spatial organisation of tau pathology and its dependence on brain connectivity can be identified using approaches that combine tau PET and FC.

Nabizadeh (2024) [21] has thus shown that FC between these two types of regions decreases as tau spreads. This reduction is more pronounced in the entorhinal cortex

and the hippocampus, which are essential for memory and decision-making. The combination of proteins disrupts FC even more significantly [21].

This gradual alteration in connectivity can also be quantified by examining the relationship between connectivity-based distance from tau epicentres and tau accumulation over time, showing a progressive decrease in connectivity as pathology spreads (see Figure 3.3).



(a) Hypothetical propagation of tau using functional connections.

(b) Correlation between distance based on functional connections in groups.

Figure 3.3: Spread of tau through FC. Adapted from [21]

The results discussed highlight the importance of FC in disease progression and the potential for using it as an early biomarker to monitor this progression before the onset of major clinical symptoms [15, 20, 21].

3.3 Current limitations

Despite recent advances in our understanding of tau propagation and its impact on brain connectivity, several limitations remain in current studies combining tau PET imaging and FC. These methodological challenges relate mainly to inter-individual variability, the complexity of the underlying interactions between tau and $A\beta$, and the difficulties involved in accurately modelling tau progression in the brain.

3.3.1 Inter-individual variability in tau and $A\beta$ propagation

A major limitation is the inter-individual variability in tau and $A\beta$ accumulation profiles. Although studies such as that by Schultz et al. (2017) [20] have identified clear patterns of tau propagation in specific networks, there remains a high degree of variability even among clinically normal individuals [15]. Some individuals exhibit atypical patterns of tau spread, which complicates the interpretation of results at the population level. Moreover, genetic factors such as the APOE gene and the presence of comorbidities

influence the progression of tau, making it difficult to generalise the outcomes [20]. For example, atypical clinical forms like Progressive Non-fluent Aphasia (PNA) and Posterior Cortical Atrophy (PCA) can influence the dynamics of tau propagation and modulate FC in different ways across clinical groups and disease stages [20].

3.3.2 Methodological and technical limitations

Another limitation is the difficulty in accurately modelling the FC between brain regions affected by tau and $A\beta$. Although advanced approaches have made it possible to visualise disruptions in neural networks, they still struggle to capture the complexity of the interactions between tau, $A\beta$, and neural networks. For example, the ESM model used by Schultz et al. (2017) [15] does not capture the molecular mechanisms underlying propagation, like the effects of glial cells and microglia. Moreover, functional network analysis based on rs-fMRI, such as that conducted by Sintini et al. (2021) [20], does sometimes fail to clearly distinguish the contributions of tau propagation from those of other pathological factors, such as non-AD proteinopathies or vascular pathology.

Methodological limitations also include the spatial resolution of tau PET imaging and the difficulty of linking FC data with more specific information about tau progression in some brain regions. Although studies similar to those conducted by Nabizadeh (2024) [21] have shown that FC between tau epicenter regions and non-epicenter regions decreases with the accumulation of tau, this reduction remains difficult to quantify precisely. The spatial resolution of tau PET imaging is a limiting factor, because it does not always allow for the precise distinction between small regions affected by tau accumulation and adjacent areas that are not yet affected, mainly due to spill-in and spill-out effects, corresponding to signal contamination between neighbouring regions (see Appendix B.2) [21, 31].

3.3.3 Challenges for early biomarker identification

Finally, a significant limitation of current studies concerns the monitoring of tau progression during the preclinical stage of the disease, before the clinical symptoms. Even though changes in FC have been observed in the early stages, it remains difficult to link these changes to specific biomarkers of tau progression [15, 20]. FC patterns vary widely among individuals, and although several studies have shown that these early changes may predict disease progression, rs-fMRI-based biomarkers are not yet reliable enough for widespread clinical use.

Part II

Experimental Study

Chapter 4

Materials and methods

4.1 Study population and multimodal dataset

The entire dataset includes 220 subjects, of whom 111 had matched multimodal data (tau PET and rs-fMRI collected within 371 days of each other, see Section 4.2), and were thus used in the analyses detailed here. For this study, participants were grouped into three clinical categories obtained through multidisciplinary clinical review integrating cognitive assessments, biomarkers, and clinical evaluation:

- CN: amyloid-negative CN individuals¹; preclinical AD participants and CN individuals without available amyloid status;
- MCI: patients who showed a cognitive deficit on neuropsychological testing, defined as prodromal AD in the context of this cohort;
- DEM: Alzheimer’s dementia.

It must be pointed out that the CN group is, by construction, a heterogeneous group including subjects who are amyloid-negative, subjects with preclinical AD (amyloid-positive but CN), and subjects for whom information regarding amyloid status is unavailable. Although this classification is necessary due to the limitations of the dataset, this may introduce biological heterogeneity within the CN group and reduce the ability to detect group differences. Conducting sensitivity analysis restricted to amyloid-negative CN subjects could be necessary to fully control for this limitation, but was not possible due to the available sample sizes (see Table 4.1).

Among the 111 participants of the multimodal dataset, 18 were classified as DEM, 43 were classified as MCI, and 22 were classified as CN. 28 individuals had no available

¹For amyloid-positive (A+) individuals: A+ CN = preclinical AD, A+ MCI = prodromal AD, A+ DEM = AD dementia.

clinical classification and were thus removed from group-level analyses but still remained in analyses that did not require clinical categorisation. The demographic and clinical characteristics of this sample are summarised in Table 4.1.

Table 4.1: *Demographic and clinical characteristics of the multimodal cohort.*

Variable	Total cohort	CN	MCI	DEM	Unclassified
Participants, n	111	22	43	18	28
Age at PET, years	70.6 ± 8.9	68.1 ± 8.7	72.8 ± 8.7	68.9 ± 8.5	70.1 ± 9.1
Female sex, n (%)	63 (56.8%)	15 (68.2%)	26 (60.5%)	11 (61.1%)	11 (39.3%)
Education, years	15.6 ± 4.0	16.4 ± 4.2	15.4 ± 3.7	12.4 ± 3.4	17.3 ± 3.4
MMSE	25.6 ± 4.0	29.0 ± 1.0	26.3 ± 1.7	18.7 ± 3.6	25.9 ± 3.7

Values are presented as the mean $\pm$ standard deviation unless otherwise stated. Sample size may vary between columns because of missing data. Age was calculated based on the date when the PET was acquired. MMSE stands for Mini-Mental State Examination.

In sections 5.1 and 5.7, and for the inter-regional tau correlation analysis (Figure 5.6), the analyses were conducted on the full PET dataset ($n = 220$; 86 CN, 55 MCI, 24 DEM, and 55 unclassified), independently of rs-fMRI availability. All other analyses were restricted to the matched multimodal subsample ($n = 111$) described above.

4.1.1 rs-fMRI data

The rs-fMRI data that are used in this study were acquired using a 3 Tesla GE SIGNA™ Premier scanner (General Electric Healthcare, Chicago, Illinois). Functional images were obtained with a T2-weighted gradient-echo Echo-Planar Imaging (EPI) sequence using the following parameters: Repetition Time (TR) = 1700 ms or 1500 ms, Echo Time (TE) = 30 ms, flip angle = 90° , voxel size = $1.7188 \times 1.7188 \times 2.0 \text{ mm}^3$, Field of View (FOV) = $220 \times 220 \text{ mm}^2$, acquisition matrix = 110×110 , and 75 axial slices. A total of 217 or 250 functional volumes were acquired for each session. In addition, a multiband acceleration factor of 3 and a parallel imaging acceleration factor of 2 were applied to optimise temporal resolution while maintaining adequate spatial coverage. The details of which subjects and sessions correspond to which TR can be found in Appendix A.1.

rs-fMRI data were preprocessed using the automated pipeline fMRIPrep 25.2.3 (Esteban et al., 2019) [32], based on Nipype 1.10.0. Anatomical preprocessing included intensity non-uniformity correction, skull stripping, brain tissue segmentation (grey matter, white matter, and CSF), cortical surface reconstruction, and spatial normalisation to the MNI152NLin2009cAsym template.

Functional preprocessing included motion correction, co-registration to anatomical

images, spatial normalisation, and extraction of nuisance regressors. Several confounding signals were estimated, including motion parameters, framewise displacement, Derivative of RMS Variance over voxels (DVARs), global signals, and CompCor physiological regressors [33]. Motion outlier volumes were identified based on framewise displacement and DVARs thresholds.

Detailed information regarding the preprocessing workflow is provided in Appendix C.1.

Initially, a cohort of 173 participants was included in the rs-fMRI dataset. However, 12 participants were excluded due to issues relating to data collection or pre-processing (see Figure 4.1).

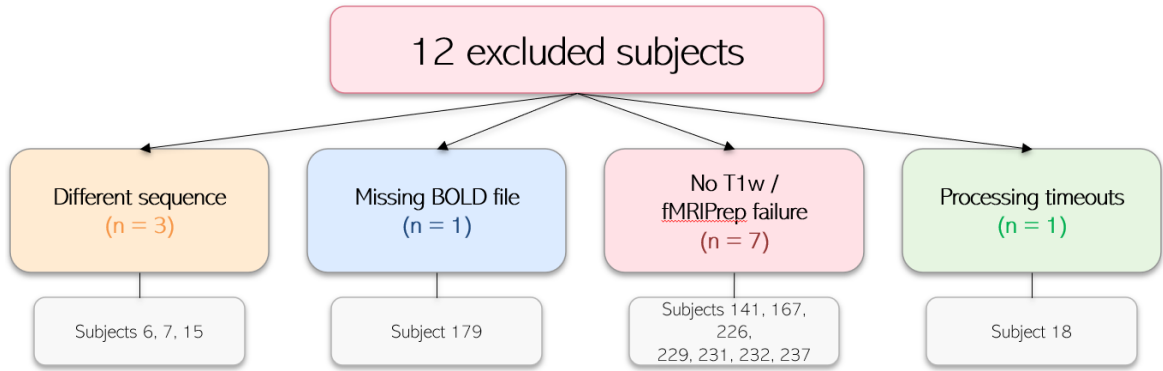


Figure 4.1: Flowchart showing the exclusion criteria applied to the rs-fMRI dataset.

4.1.2 Tau PET data

[18F]MK-6240 (Lantheus Inc.) is a tau imaging agent designed to detect tau tangles in the brain, used as part of an exploratory study into AD. The radiosynthesis process was carried out at KULeuven and the agents were shipped to the clinic. Seventy minutes after intravenous administration of [18F]MK-6240 (target activity = 185 ± 5 MBq), a 30-minute dynamic scan was performed using a Philips Vereos digital PET-CT scanner. The images were reconstructed using the manufacturer’s standard algorithm, including correction for attenuation, scattering and decay, as well as time-of-flight information. A Point Spread Function (PSF) and 1 mm resampling were also applied to improve resolution recovery.

For each participant, tau PET images were co-registered with a T1-weighted (T1w) image using the PetSurfer pipeline [34, 35], a set of tools integrated into FreeSurfer that enables end-to-end combined MRI-PET analysis. SUVR values were normalised using the cerebellar cortex as reference region, which has been shown to be relatively spared from tau pathology across AD stages. They were extracted for all 68 cortical regions of the Desikan-Killiany atlas using the fs_suvr_ctx columns generated by FreeSurfer,

which provided the primary tau measures used in all subsequent analyses.

Longitudinal tau accumulation

Participants with at least two available tau PET acquisitions were used for the longitudinal study of tau PET data (see section 5.7), resulting in 23 participants: 13 CN and 10 MCI. The annualised rate of change in global tau SUVR was computed as:

$$\Delta\text{SUVR} = \frac{\text{SUVR}_{d_2} - \text{SUVR}_{d_1}}{(d_2 - d_1)/365}$$

with d_1 and d_2 being the dates of the first and last PET acquisition in days.

4.1.3 Neuropsychological assessment

The neuropsychological assessment carried out in this study [36] focused on four main cognitive domains: verbal episodic memory, language, executive functions, and visuospatial functions. Verbal episodic memory was measured using the Free and Cued Selective Reminding Test (FCSRT), French version [36]. Language was assessed using the Lexis Naming Test and verbal fluency tests, including categorical fluency for animals and the letter ‘P’ [36]. Executive functions were measured using the Trail Making Test (TMT) (parts A and B) and Luria’s Graphic Sequences [36], while visuospatial functions were assessed using the Clock Drawing Test [37] and the Praxis section of the CERAD battery [36].

For each cognitive domain, composite scores in the form of Z-scores were calculated, using as a reference an independent sample of 32 cognitively healthy participants ($A\beta^-$), with Mini-Mental State Examination (MMSE) scores $\geq 26/30$, followed for 8 years (data collected in the UCL-2010–412 study). This sample served as the standard for assessing the cognitive performance of participants in our study. The $A\beta^-$ CN participants included in our sample were of a similar age and had similar MMSE scores to those in the reference sample. A cognitive domain was considered impaired if its Z-score was less than -1.5 standard deviations (SD). Participants were classified as having MCI if at least one cognitive domain showed impairment. Conversely, participants were considered CN when all their Z-scores were above the threshold of -1.5 SD.

4.2 Matching of PET, fMRI and neuropsychological sessions

Tau PET and rs-fMRI scans are not always acquired on the same day for each participant. To correctly match the data from each modality (PET and functional magnetic resonance

imaging (fMRI)) and eventually carry out a longitudinal study, it was necessary to match sessions based on temporal proximity.

The dates of the PET scans were compared with those of the MRI scans and neuropsychological assessments to obtain a temporal relationship. This alignment was done by limiting the period between each participant’s sessions to no more than 371 days (approximately one year). This threshold was chosen as a pragmatic compromise between maximizing the number of matched multimodal sessions and minimizing the temporal mismatch between modalities. A stricter window would have substantially reduced the number of usable matched sessions, particularly for participants with irregular visit schedules, while a longer window would have introduced greater uncertainty regarding the correspondence between tau burden and FC at the time of each acquisition. Similar one-year windows have been used in previous multimodal AD studies [38, 39].

4.3 Region of Interest (ROI) definition and time-series extraction

4.3.1 Desikan-Killiany atlas

Table 4.2: *ROIs within the cortex according to the Desikan-Killiany atlas.*

ROI	ROI
Banks of Superior Temporal Sulcus	Parahippocampal
Caudal Anterior Cingulate	Pars Opercularis
Caudal Middle Frontal	Pars Orbitalis
Cuneus	Pars Triangularis
Entorhinal	Pericalcarine
Frontal Pole	Postcentral
Fusiform	Posterior Cingulate
Inferior Parietal	Precentral
Inferior Temporal	Precuneus
Insula	Rostral Anterior Cingulate
Isthmus Cingulate	Rostral Middle Frontal
Lateral Occipital	Superior Frontal
Lateral Orbitofrontal	Superior Parietal
Lingual	Superior Temporal
Medial Orbitofrontal	Supramarginal
Middle Temporal	Temporal Pole
Paracentral	Transverse Temporal

Originally introduced by Desikan et al. (2006)[40], the Desikan-Killiany atlas segments the cortical surface into 68 ROIs (34 per hemisphere), each representing an anatomical subdivision of the cerebral cortex based on the gyri. It is a cortical parcellation scheme resulting from a morphometric analysis using surface-based MRI data from a large

sample of healthy adults.

The atlas labels cover the main cortical regions associated with specific cognitive functions, such as memory, language and executive functions. Regions in the left hemisphere are identified by IDs ranging from 1000 to 1999, while those in the right hemisphere are identified by IDs ranging from 2000 to 2999.

This atlas was used for this study as regional fs_suvr values provided by the laboratory were already calculated using this model. The 68 cortical regions covered in this study are listed in Table 4.2 and illustrated in Figure 4.2.

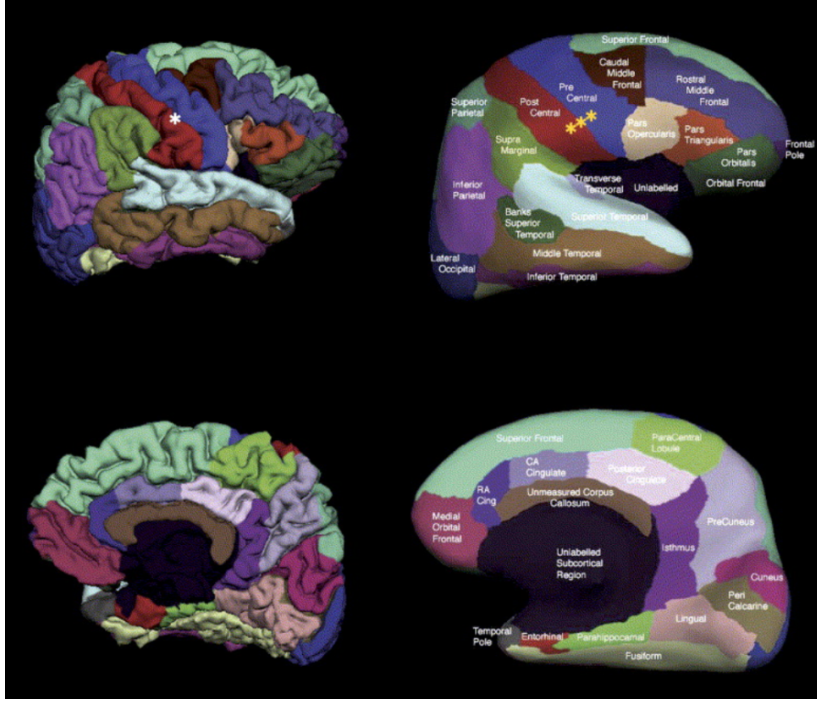


Figure 4.2: *Desikan-Killiany cortical parcellation depicting lateral and medial views of one hemisphere. Left column represents the pial surface whereas right column represents the inflated cortical surface. From [40]*

4.3.2 Time-series extraction

Time series for the ROIs were extracted from the pre-processed functional data using the Desikan-Killiany atlas. This process consisted of several steps: the Desikan-Killiany parcellation image was transformed and resampled onto the BOLD data grid to ensure spatial alignment. Next, only the cortical regions of the Desikan-Killiany atlas were extracted, excluding undefined regions (labels 1000 and 2000). Labelling was carried out using the FreeSurfer colour lookup table, which enabled the numerical labels of each region to be mapped to meaningful region names. The atlas was relabeled with contiguous values (1..N) to make it compatible with the NiftiLabelsMasker tool from the Nilearn library [41] used to extract the time series. For each ROI, the time series

was obtained by averaging the BOLD signals from all the voxels present in that region, giving one representative BOLD signal for each ROI.

Global Signal Regression (GSR) was deliberately not applied in this study. Although GSR can reduce the influence of non-neural global fluctuations, it is known that it can cause artificial anticorrelations between brain regions, which can distort the estimation of FC and obscure genuine network organisation [42]. Given that the present study focuses on pairwise connectivity relationships and graph theory metrics, applying GSR could have biased the results by artificially reducing connectivity strength across the board. This choice is consistent with recent recommendations for FC studies in clinical populations [43, 44].

Regarding temporal filtering, a high-pass filter at 0.005 Hz was applied with no additional low-pass filtering. Although band-pass filtering around 0.01-0.1 Hz is commonly used in resting-state fMRI [45, 46], the TR of this dataset (1.5-1.7 s) remains insufficient to reliably separate all physiological fluctuations from the low-frequency range of interest. Physiological noise was therefore partly addressed through mean CSF signal regression and motion parameters [47].

The detailed extraction workflow is provided in Appendix C.2.

4.3.3 Confound regression

When extracting time series data and analysing FC, it is important to consider confounds (or confounding variables), which are unwanted factors that can alter the results of brain analyses.

In order to account for these effects and improve the accuracy of the results, we extracted several confounding factors using the confounding factor files generated by fMRIPrep. This mainly included information on head motion (translation and rotation) and the average CSF signal as a proxy for physiological noise. More specifically, the following variables were extracted and used for data correction:

- Translation (`trans_x`, `trans_y`, `trans_z`): movements of the head along the X, Y and Z axes.
- Rotation (`rot_x`, `rot_y`, `rot_z`): rotations of the head around the X, Y and Z axes.
- CSF: Average signal accounting for non-neuronal physiological fluctuations.

No physiological noise correction based on anatomical Component Correction (aCompCor, which derives the noise regressor from the white matter and CSF signals [33]) was performed in this work. Rather, the average CSF signal was used as a simpler

substitute for physiological noise, consistent with the somewhat conservative approach to confounds taken in this study. Such an approach prevents the addition of further degrees of freedom related to the choice of aCompCor components, at the cost of potentially less complete physiological noise reduction.

4.4 FC and graph theory analysis

4.4.1 Construction of connectivity matrices

For this study, FC matrices were constructed using ROI-averaged time series derived from fMRI data. This is an important step in analysing connectivity between different cortical regions of the brain.

To construct the connectivity matrices, the time series averaged by ROI were used to compute a static correlation matrix showing the correlations between the ROIs without taking time lags into account. This step allows determining the instantaneous functional relationships between the regions.

SCA analyses were subsequently performed for all pairs of ROIs. The lag was varied between -12 and +12 TR [29], thus making it possible to study correlations between ROIs at different time lags. In order to determine whether this window is appropriate, we checked the distribution of the optimal lags for all ROI pairs and participants (Figure 4.3). It has been shown that the largest correlation between ROIs occurred 73% of the time at a lag of 0 TR, thus proving that the window used was wide enough to cover the optimal lag.

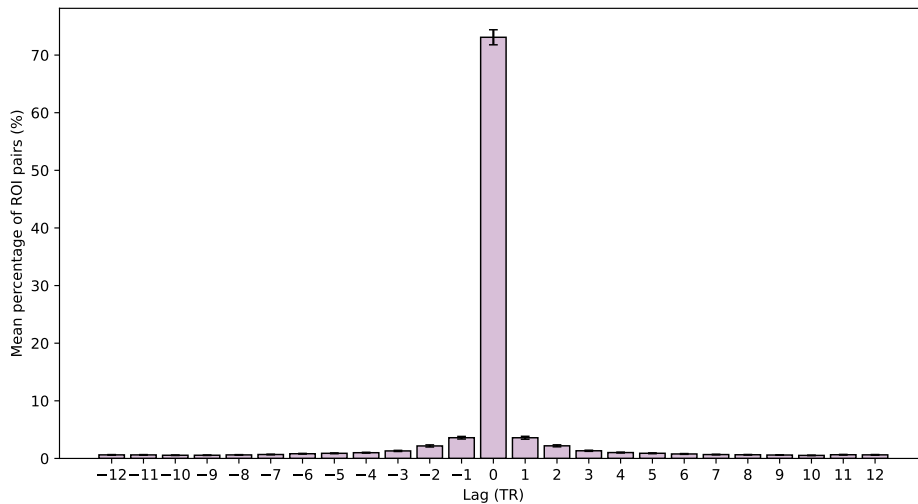


Figure 4.3: Mean lag values distribution across the multimodal dataset. Bars correspond to the mean percentage of ROI pairs for each lag value, and error bars indicate the standard error of the mean.

The resulting matrices were divided into two types: (i) a static correlation matrix, representing the instantaneous relationship between regions at lag 0, and (ii) a dynamic correlation matrix representing the signed correlation at the lag of maximal absolute cross-correlation, as well as the lags associated with these maximum values. The choice of using the maximal absolute cross-correlation across all lags as opposed to the typical lag-0 Pearson correlation was made to account for time-delayed interactions between the regions, an approach that might be particularly relevant in the case of network-based propagation of tau. However, it must be pointed out that such a strategy is prone to overestimating connectivity measures between those regions that have low instantaneous correlations and false positive peaks at far lags. The algorithm used is summarised in Algorithm 4.4.1.

Algorithm **FC matrix construction** *Section 4.4.1*

Input $\mathbf{X}_{\text{clean}} \in \mathbb{R}^{T \times 68}$

Output $\mathbf{FC}_0$ (68×68) · $\mathbf{SCA}$ (68×68) · $\mathbf{L}$ (68×68)

1. Load cleaned ROI time series from CSV file.
2. Compute static lag-0 connectivity: $\mathbf{FC}_0 = \text{corrcoef}(\mathbf{X}_{\text{clean}})$.
3. For each ROI pair (i, j) with $j \geq i$, test lags $k \in [-12, +12]$ TR.
4. Calculate lagged cross-correlations: $\text{CC}_{ij}(k) = \text{corr}(x_i, x_j \text{ shifted by } k)$.
5. Select lag of maximal absolute correlation: $k^* = \arg \max_k |\text{CC}_{ij}(k)|$.
6. Signed SCA value: $\mathbf{SCA}_{ij} = \text{CC}_{ij}(k^*)$ and $\mathbf{SCA}_{ji} = \mathbf{SCA}_{ij}$.
7. Associated lag: $\mathbf{L}_{ij} = k^*$ and $\mathbf{L}_{ji} = -k^*$.
8. Save $\mathbf{FC}_0$, $\mathbf{SCA}$ and $\mathbf{L}$ matrices.

Dynamic connectivity matrices were subsequently used in the analyses.

4.4.2 Graph theory metrics

This study uses multiple indicators derived from graph theory applied to connectivity matrices to analyse the FC of the brain. These metrics include the degree, the clustering coefficient, and both Local Efficiency (E_l) and Global Efficiency (E_g), each of which allows for a better understanding of the functional brain network, exploring how the ROIs connect and interact.

The degree (or ‘strength’) of a node in a network represents the sum of the weights of the connections from that node to all other nodes. Formally, the strength of node i is

defined as:

$$s_i = \sum_{j \neq i} w_{ij} \quad (4.1)$$

where w_{ij} denotes the FC weight between regions i and j . Regions with a high degree, often referred to as “functional hubs”, play a central role in the organisation of the brain network, while regions with a low degree are considered more peripheral. This metric is particularly useful for identifying important brain regions involved in complex cognitive processes. Degree graphs are often used to analyse how certain brain regions are more or less involved in global functional interactions.

The clustering coefficient of a region measures the extent to which its neighbours are interconnected. For a weighted network, it is formally defined as:

$$C_i = \frac{1}{s_i(m_i - 1)} \sum_{j,h} \frac{(w_{ij} + w_{ih})}{2} a_{ij} a_{ih} a_{jh} \quad (4.2)$$

where $m_i = 67$ is the number of neighbours of node i , j and h are two distinct neighbours of the node, s_i its strength as defined in Equation 4.1, w_{ij} the weight of the connection between nodes i and j , and a_{ij} the corresponding entry of the binary adjacency matrix ($a_{ij} = 1$ if $w_{ij} > 0$, 0 otherwise). A high clustering coefficient indicates that a region’s neighbours form a dense cluster of connections, reflecting a strong local organisation. Conversely, a low clustering coefficient suggests that a region’s neighbours are sparsely connected, implying a looser structure within the network. This measure allows us to assess the local organisation of the brain network, which is relevant for understanding how information is processed within local networks.

E_l and E_g are other critical metrics that measure, respectively, the efficiency of communication within subsets of the network (local) and across the entire network (global). E_g is measured by taking the mean of inverse shortest paths between all pairs of nodes, while E_l measures the efficiency of communication within the neighbourhood of each node [48]:

$$E_{\text{glob}} = \frac{1}{N(N-1)} \sum_{i \neq j} \frac{1}{L_{ij}} \quad \text{and} \quad E_{\text{loc}} = \frac{1}{N} \sum_i E_{\text{glob}}(G_i) \quad (4.3)$$

where N is the number of nodes, L_{ij} the shortest weighted path length between nodes i and j (computed via Dijkstra’s algorithm on the distance graph $d_{ij} = 1/w_{ij}$), and G_i the subgraph formed by the direct neighbours of node i . These two measures are integral to understanding not only communication within specific parts of the brain but also the functional integration between different regions of the brain network.

For efficiency metrics, negative edge weights were excluded prior to graph construction, following recommendations for weighted graph analysis in neuroimaging [19]. For node

degree, the algebraic sum of weights was retained to reflect net functional influence. For clustering coefficient, the weighted implementation of NetworkX was applied to the connectivity matrices.

These metrics were calculated for each subject using the dynamic correlation matrices.

Hierarchical clustering of regional connectivity profiles

For detecting clusters of cortical regions having common clustering coefficient profiles among the participants, agglomerative hierarchical clustering analysis was performed on the inter-regional correlation matrix of clustering coefficients based on Ward’s linkage criterion and a correlation-based distance metric ($d = 1 - r$), in which r stands for the Pearson correlation between the regional clustering coefficient profiles across participants. This is a standard approach for this type of analysis [49].

Tertiles of mean node degree

The cortical regions were grouped into three categories based on tertiles of their mean node degree. In the current dataset, low node degree was defined as ≤ 21.037 , mid node degree was defined as $21.037 < \text{degree} \leq 26.440$, and the high node degree was above 26.440. This grouping was used to test whether the load of tau differs depending on the degree of hubs in the cortex.

4.4.3 Tau burden measures and derived analyses

For investigating whether tau-connectivity relations differed at different spatial stages of tau disease, tau burden was calculated independently in three groups of cortical areas. These groups were defined as Braak-inspired stage regions, based on the anatomical progression of tau pathology described in the literature [6, 8, 9, 23] and on the tau PET signal observed in our dataset (Section 5.1):

- Early-stage (Braak I–II): entorhinal cortex, parahippocampal gyrus, and temporal pole;
- Intermediate-stage (Braak III–IV): inferior temporal cortex, middle temporal cortex, fusiform gyrus, and banks of the superior temporal sulcus;
- Late-stage (Braak V–VI): precuneus, isthmus cingulate cortex, posterior cingulate cortex, inferior parietal cortex, superior parietal cortex, lateral occipital cortex, lateral orbitofrontal cortex, medial orbitofrontal cortex, rostral middle frontal cortex, caudal middle frontal cortex, and superior frontal cortex. This selection was based on the broader involvement of the DMN and associative networks, which support the theory that tau pathology spreads through interconnected brain networks [11, 20].

In each stage, the average tau SUVR within the relevant regions was calculated for each subject.

Tau-connectivity spatial similarity

The similarity between the spatial patterns of tau pathology and the structure of functional brain networks was assessed by computing the pairwise similarity of tau pathology. First, for each region of the cortex, a tau profile was generated that consisted of the vector of the SUVR values of tau within each subject, resulting in a vector of size n . Then, the pairwise similarity between the tau pathologies of two regions was calculated as the Spearman correlation between the vectors obtained for each region, indicating the degree to which two brain regions have similar distributions of interindividual tau deposits. This led to the generation of a 68×68 matrix representing the pairwise similarity of tau pathology.

Resting-state network assignment For examining the effects of the relationship between tau and connectivity on different large-scale functional brain networks, cortical ROIs were assigned to four distinct anatomico-functional network categories:

- DMN: precuneus, posterior cingulate cortex, isthmus cingulate cortex, inferior parietal cortex, medial orbitofrontal cortex;
- Frontal network: superior frontal cortex, rostral middle frontal cortex, caudal middle frontal cortex, frontal pole;
- Limbic network: entorhinal cortex, parahippocampal gyrus, temporal pole;
- Visual network: cuneus, lingual gyrus, lateral occipital cortex, pericalcarine cortex.

Such categorisation was guided by functional parcellation data available in the literature [50, 51], and it was modified according to the regions used in this study that are based on the Desikan-Killiany atlas.

The node degree analysis included grouping ROIs into broader anatomical classes, making it easier to visualise any regional patterns present. ROIs were placed in one of seven groups: frontal (superior frontal cortex, rostral middle frontal cortex, caudal middle frontal cortex, lateral orbitofrontal cortex, medial orbitofrontal cortex, frontal pole, pars opercularis, pars orbitalis, pars triangularis, precentral gyrus), temporal (banks of the superior temporal sulcus, fusiform gyrus, inferior temporal cortex, middle temporal cortex, superior temporal cortex, transverse temporal cortex), parietal (inferior parietal cortex, superior parietal cortex, supramarginal gyrus, postcentral gyrus, precuneus, paracentral lobule), occipital (cuneus, lateral occipital cortex, lingual gyrus, pericalcarine cortex), cingulate (caudal anterior cingulate cortex, rostral anterior cingulate cortex, posterior cingulate cortex, isthmus cingulate cortex), limbic (entorhinal cortex,

parahippocampal gyrus, temporal pole), or insular (insula) regions.

This was done only for the purpose of colouring of the scatter plot (Figure 5.4), and had no impact on the Spearman correlation value calculated.

4.4.4 Seed-based analysis

In order to find out if the connectivity network of a cortical region is capable of predicting the distribution of tau load, seed-based connectivity analyses were performed for all 68 cortical regions to select the seeds with the highest Spearman correlation.

For each of the 68 brain regions considered as a potential seed region, the Spearman correlation of its FC pattern with the mean regional tau SUVR was computed separately for each clinical group. Figure 5.15 shows the ten most correlated seeds across the three groups. The first one was then used as a reference region.

For the investigation of the relative influence of FC and anatomical distance, the next step involved conducting seed-based linear regression analysis, using the reference region. Tau burden in target cortical areas was modelled according to either anatomical distance from the reference region, strength of FC with the reference region, or their combination.

To further examine the inter-individual variability of the connectivity-tau relationship, individual associations between seed-based connectivity and regional tau load were calculated separately for each subject.

4.5 Statistical analyses

Statistical analyses were done in order to test hypotheses on the difference in connectivity between the groups and to establish the relationship between the measurements of tau and connectivity in the brain. Non-parametric methods were used to test all groups because of the non-normal distribution of most variables. The significance level adopted was $\alpha = 0.05$.

4.5.1 Statistical tests

Group comparisons

The Kruskal-Wallis H test, a non-parametric statistical test, was used to compare FC differences between different clinical groups, which can be used when there are more than two groups that need to be compared. The advantage of the Kruskal-Wallis H test is that it does not require data to be normally distributed, as well as variance homogeneity. The Mann-Whitney U test was then applied to carry out pairwise comparison for two

groups when the test was significant at $p < 0.05$. This non-parametric test compares ranks between two samples.

In order to examine associations among continuous variables, Spearman rank correlations (ρ) were used for correlation analyses.

Multiple linear regression

In order to determine the independent effects of global tau burden, age, gender, and years of education on FC, multiple regression models were calculated based on each of the four graph theory measures (E_g , E_l , average clustering coefficient, average node degree).

Multiple comparison correction

Two correction methods were applied:

- Bonferroni correction: used in the post-hoc pairwise comparisons of groups (three comparisons) and between the groups with different tertile values of node degree (three groups);
- Benjamini-Hochberg False Discovery Rate (FDR) correction: used for multiple comparisons, such as simultaneous tests across all 68 ROIs and the seed-based analysis.

In contrast to the Bonferroni approach, the FDR correction technique is not as conservative, thus enabling control over the false positive rate without sacrificing power.

Permutation test

In the case of tau-connectivity spatial similarity analysis, the traditional p-values calculated using the Spearman correlation are anticonservative as a result of the lack of independence among the pairs of regions (as every region contributes to 67 pairs). Statistical significance was assessed through the use of a permutation test, where the labels of the regions were shuffled 10,000 times, Spearman correlation was computed again for each shuffle, and empirical p-values were set as the proportion of permuted correlations exceeding the observed value.

4.5.2 Tau accumulation across clinical groups

The global cortical tau burden (measured by mean SUVR from all 68 cortical ROIs) was compared between the CN group, MCI group, and DEM group with a Kruskal-Wallis test, and then analysed with Mann-Whitney post-hoc tests. For regional analysis, the four medial temporal ROIs with greatest tau burden (entorhinal cortex, parahippocampal gyrus, inferior temporal cortex, and fusiform gyrus) were selected for comparison with

the same statistical methods, which is consistent with the typically affected regions during the early stage of AD pathology and subsequent temporal spread of tau in AD [8, 9].

4.5.3 Regional tau distribution and network topology

For determining correlation between regional tau burden and network topology, Spearman correlation coefficients were computed for regional tau SUVR and mean node degree for all 68 cortical regions. After that, to compare the regional tau burden among the three tertiles of node degree, Kruskal-Wallis and then Mann-Whitney comparison analysis were performed.

4.5.4 Graph theory metrics across clinical groups

E_g , E_l , mean node degree, and mean clustering coefficients were analysed between the three clinical groups using the Kruskal-Wallis test followed by pairwise Mann-Whitney comparisons with Bonferroni correction. The regional clustering coefficients were also compared between the three groups using Kruskal-Wallis tests separately for the 68 different ROIs, adjusting for multiple comparisons using the FDR method. The 15 ROIs having the smallest FDR-corrected p-values are shown in Figure 5.8.

4.5.5 Relationship between tau burden and FC

Spearman correlations between global tau burden and all four graph metrics were also calculated. Multiple regression models including age, gender, and education were used to determine the relationship between global tau burden and graph connectivity measures after controlling for these confounding variables. Stage-specific Spearman correlations between early, intermediate, and late stage tau burden and all four graph metrics were performed with p-values adjusted using FDR correction.

4.5.6 Tau-connectivity spatial similarity

The Spearman correlation coefficient between the pairwise tau similarity matrix and the pairwise FC matrix was calculated both for the entire dataset as well as separately for each of the clinical groups and RSNs. The statistical significance was estimated based on the permutation test described in Section 4.5.1.

4.6 Technical resources

Some technological and linguistic tools have been used to support this work. Image visualisation and validation were conducted with MRICroGL software. Computational

analyses and graph plotting were carried out using Python. Linguistic assistants such as DeepL and NotebookLM were applied for translating and reformulating scientific content. Coding assistants including Claude and ChatGPT were used for coding and debugging Python programs.

Computational resources were provided by the Consortium des Équipements de Calcul Intensif (CECI), funded by the Fonds de la Recherche Scientifique de Belgique (F.R.S.-FNRS) under Grant No. 2.5020.11 and by the Walloon Region.

All processing and analysis scripts are publicly available at: https://github.com/Reb999/AD_tau_fmri_thesis_code

Chapter 5

Results

In this chapter, the results of the multimodal analysis performed to investigate the association between tau pathology and FC in the brains of patients with AD are presented.

5.1 Tau accumulation across clinical groups and brain regions

Tau accumulation was analysed in all three clinical groups (CN, MCI, DEM) through a two-step approach, which first included a global analysis of overall cortical tau deposition across the groups, followed by a regional analysis focused on the brain regions with the highest deposition levels.

Statistical analysis performed using the Kruskal–Wallis test (Table 5.1) revealed statistically significant differences in global cortical tau burden across groups ($H = 95.70$, $p = 1.65 \times 10^{-21}$). Subsequent post-hoc pairwise comparisons using Bonferroni correction demonstrated statistically significant differences between CN vs MCI, CN vs DEM and MCI vs DEM ($p < 0.001$ for all pairwise comparisons). The strongest increase in tau deposition appeared to occur between the CN and MCI stages, whereas the transition from MCI to DEM was associated with a comparatively more moderate increase in global tau burden.

Table 5.1: Pairwise Mann–Whitney post-hoc tests for global cortical tau burden between different clinical groups performed after the Kruskal–Wallis test. *P* values were corrected with the Bonferroni method.

Comparison	U statistic	Bonferroni-corrected p-value
CN vs MCI	521.0	1.02×10^{-14}
CN vs DEM	16.0	5.97×10^{-13}
MCI vs DEM	271.0	7.84×10^{-5}

An increase in regional tau burden was shown to be progressively present among the different clinical stages with higher SUVR values noted in the DEM group than those in the MCI group, and the lowest in the CN group, as illustrated in Figure 5.1. The brain areas that were most affected in all groups were located in the MTL and especially included the entorhinal cortex, parahippocampal gyrus, inferior temporal cortex, and fusiform gyrus. The increase in tau accumulation was observed in most cortical regions, although the frontal and occipital lobes showed lower total tau levels.

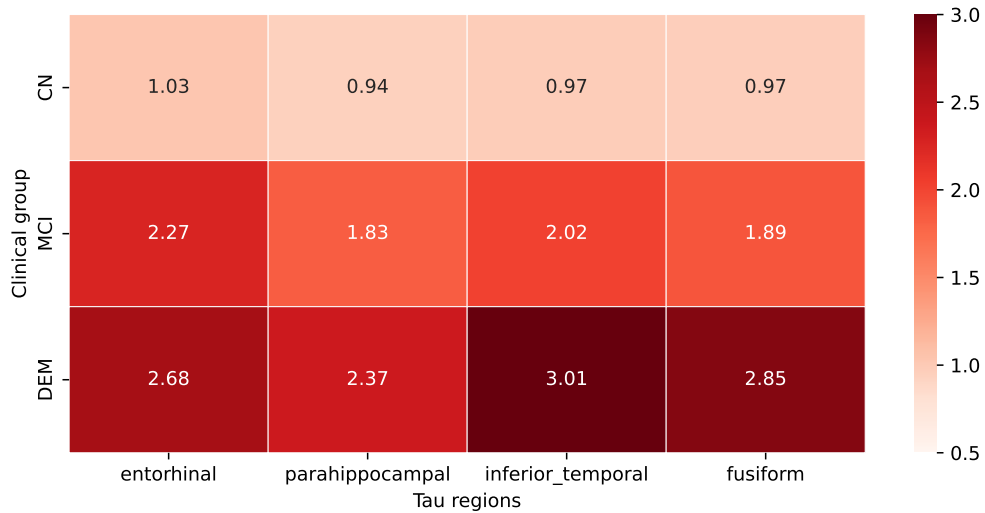


Figure 5.1: Heatmap demonstrating the mean SUVR of the tau protein in selected regions of the MTLs in the CN, MCI, and DEM patient groups. The regions were selected based on their established role in early AD pathology. The warmer the colour, the greater the regional burden of the tau protein.

Group comparisons were then made separately for each of the regions that exhibited the greatest level of tau deposition. According to the results provided in Figure 5.2, statistically significant changes were found in all four medial temporal regions (entorhinal, parahippocampal, inferior temporal, and fusiform) from CN to MCI as well as from CN to DEM ($p < 0.001$ for all comparisons after Bonferroni correction). No statistically significant difference was found between MCI and DEM regarding the

entorhinal cortex after correction ($p = 0.23$). Detailed regional statistics are provided in Appendix D.1.

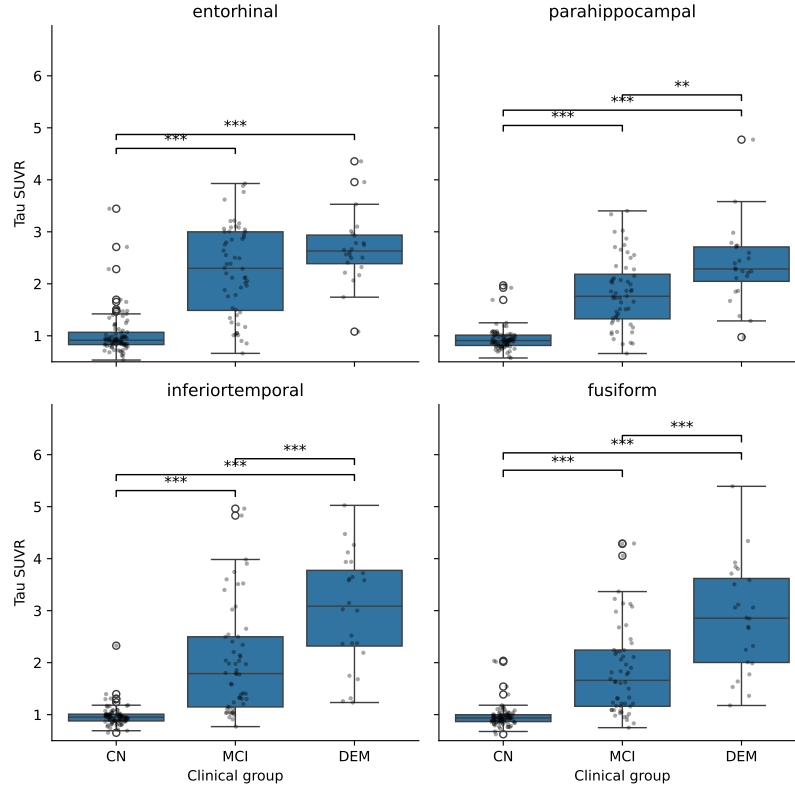


Figure 5.2: Boxplots showing the distribution of tau SUVR in clinical groups (CN - MCI - DEM) in four temporal brain regions (entorhinal, parahippocampal, inferior temporal, and fusiform cortices). Individual data points represent SUVR measurements in individual subjects while boxes show the interquartile range and median. Significance bars indicate Bonferroni corrected pairwise Mann-Whitney U tests between clinical groups (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

Figure 5.3 shows the ten cortical regions with the highest mean tau SUVR across all subjects. The CN group had a relatively low amount of tau protein within all regions studied, whereas increasing accumulation of tau was seen in both the MCI and DEM groups, especially in temporal and associative cortical regions, including the banks of the superior temporal sulcus, inferior temporal, middle temporal, fusiform, inferior parietal, precuneus, isthmus cingulate, and caudal middle frontal regions.

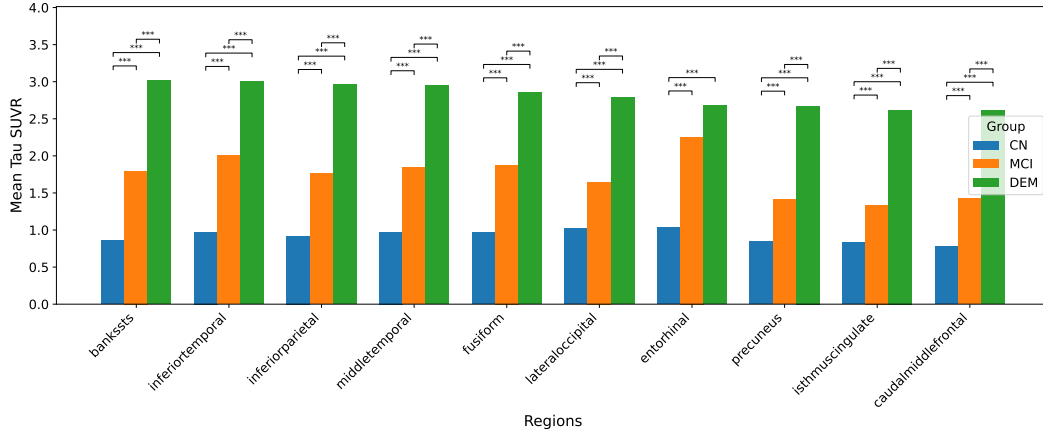


Figure 5.3: Mean Tau SUVR values of the ten regions that have the highest burden of tau among the clinical subjects. The bar graph represents mean SUVR values of the CN, MCI, and DEM subjects. Pairwise comparisons between clinical groups were analysed using the Kruskal-Wallis test, then the Mann-Whitney U test with Bonferroni correction. Significance levels ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$) are indicated by significance lines.

Regional Kruskal-Wallis tests showed significant differences between groups in all ten regions illustrated in the figure with $p_{\text{FDR}} < 0.001$ for each region. Mann-Whitney U post-hoc tests showed significant differences in tau burden between MCI and CN groups in all ten regions ($p_{\text{Bonf}} < 0.001$). DEM group also had significantly higher tau burden compared to CN group ($p_{\text{Bonf}} < 0.001$). In addition, another significant increase from MCI to dementia was observed in most of the analysed regions, specifically bankssts, inferior temporal, inferior parietal, middle temporal, fusiform, lateral occipital, precuneus, isthmus cingulate, and caudal middle frontal ($p_{\text{Bonf}} < 0.001$). The entorhinal cortex was the only exception, where both MCI and DEM showed more tau deposition compared to the CN group, while no significant difference was found between MCI and DEM after Bonferroni adjustment ($p = 0.231$).

Despite being one of the most significantly affected areas in the four-region analysis, parahippocampal gyrus is absent from the list, as its mean SUVR value does not compare to that of the neocortical brain regions on the global level. The regional statistic values can be found in Appendix D.2.

5.2 Regional tau distribution and network topology

In order to explore whether there is a correlation between tau deposition and the graph theory measures of brain network topology, the values of regional tau SUVR were examined between regions classified based on node degree, clustering coefficient, and network hubs.

Moderate Spearman correlation was found between the mean regional tau SUVR and node degree in the brain ($\rho = 0.31$, $p = 9.23 \times 10^{-3}$; Figure 5.4). The regions that showed a higher degree of tau accumulation were mostly located within temporal and limbic areas, where connectivity degree was generally moderate, with limbic regions tending toward lower degree values.

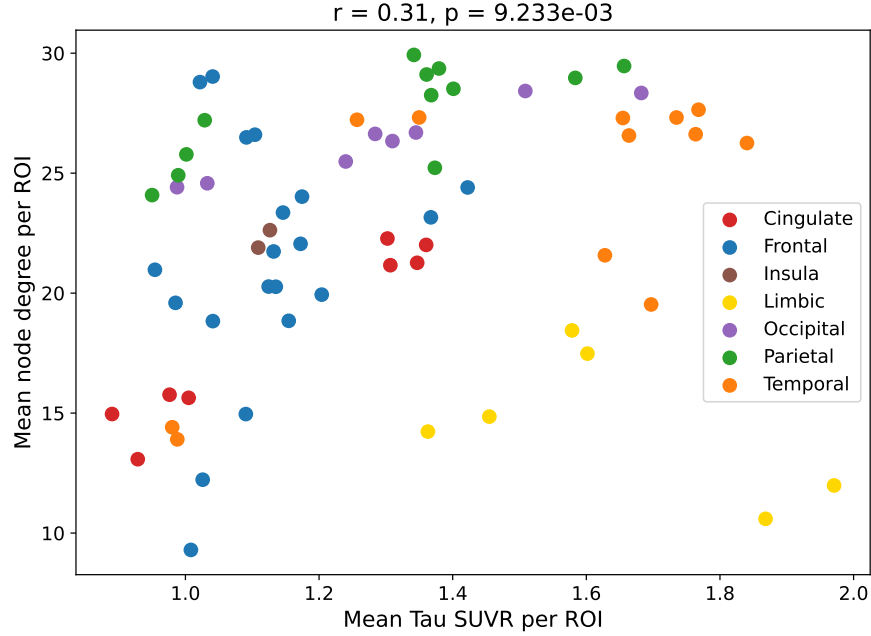


Figure 5.4: Scatter plot representing the correlation between average regional tau SUVR and average node degree for different cortical ROIs at baseline. For each ROI, tau SUVR and node degree values were averaged across the whole cohort. Each dot is an individual cortical ROI and colour-coded according to its anatomical class. Detailed anatomical classification of the cortical ROIs is presented in Section 4.4.3.

Consistent with the last correlation analysis, areas with high node degree also had greater tau burden when comparing groups stratified by their level of connectivity. As shown in Figure 5.5, the value of tau SUVR increased progressively with increasing connectivity level. The Kruskal-Wallis test showed that there were significant differences in the tau burden between the different groups based on connectivity levels ($H = 8.48$, $p = 1.44 \times 10^{-2}$). Post-hoc pairwise comparisons using Bonferroni correction indicated a significantly higher tau burden in high-degree compared to low-degree regions ($p = 3.46 \times 10^{-2}$), while differences involving medium-degree regions did not remain significant after correction.

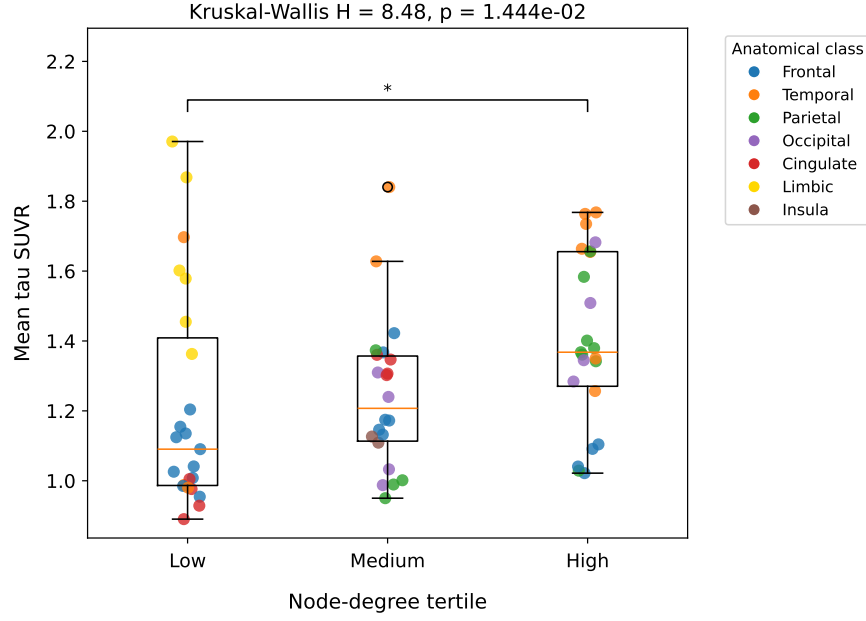


Figure 5.5: Box plots showing the mean value of tau SUVR across the cortical ROIs, categorised based on the level of node degree. The ROIs from the cortex were divided into low, medium, and high levels of node degree based on tertiles of node degree. Each dot is colour-coded according to its anatomical class. Significance bars indicate Bonferroni corrected pairwise Mann-Whitney U tests between degree-based groups (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

The full statistical outputs for group comparisons can be found in Appendix E.1.

Lastly, the inter-regional correlation architecture of tau deposition was assessed across the six regions that were most frequently impacted by tau deposition (entorhinal, parahippocampal, inferior temporal, fusiform, precuneus, and isthmus cingulate) across clinical groups. Figure 5.6 demonstrates that tau SUVR was highly correlated among anatomically adjacent medial temporal regions, where the correlation coefficients were particularly high between the inferior temporal and fusiform cortices ($r = 0.95$) and between the parahippocampal and inferior temporal cortices ($r = 0.92$). The precuneus and isthmus cingulate, on the other hand, represented a separate cluster, with weaker correlations with the medial temporal cluster, especially the entorhinal cortex.

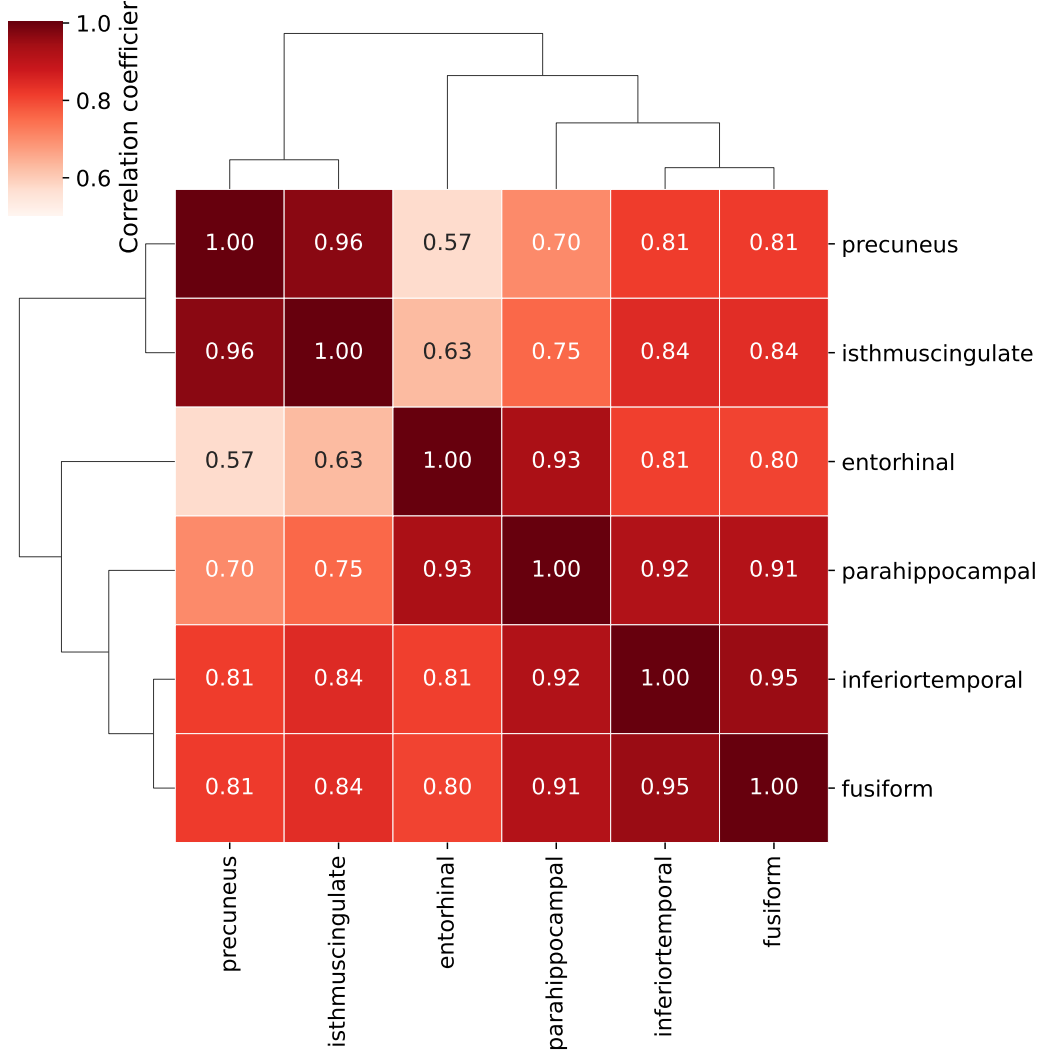


Figure 5.6: *Correlation heatmap of clusters indicating correlation structure of tau SUVR among six regions affected by tau. Warmer colours indicate higher correlations between regional burdens of tau. Lines indicate clusters of regions identified by hierarchical clustering*

5.3 Graph theory metrics of FC across groups

For each individual, graph theory measures were calculated for the FC matrices to describe the network architecture at each stage of the clinical process, including E_g , E_l , mean node degree, and mean clustering coefficient. The distribution of graph metrics is presented in Appendix E.3.

Efficiency at the global and local levels was compared for the three clinical groups. As shown in Figure 5.7, both measures showed non-linear trends depending on disease progression. E_g medians were CN = 0.382, MCI = 0.394, DEM = 0.348, indicating the pattern CN < MCI > DEM ($H = 7.36$, $p = 2.52 \times 10^{-2}$). The same trend was demonstrated for E_l , where the medians were CN = 0.403, MCI = 0.414, DEM = 0.367

($H = 7.81$, $p = 2.01 \times 10^{-2}$).

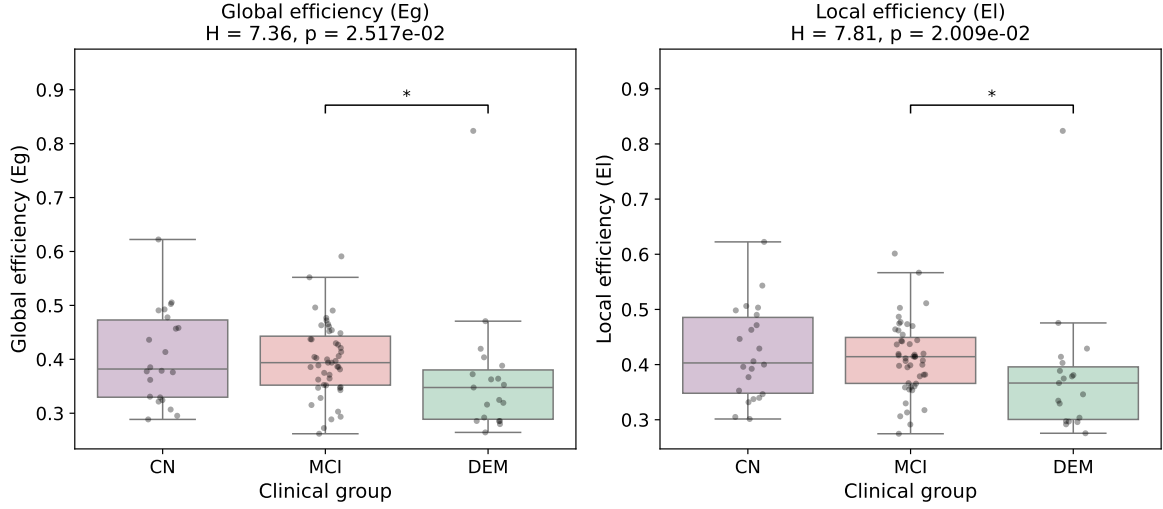


Figure 5.7: Boxplot representation of E_g and E_l according to clinical groups. Each data point represents a participant. Significance bars refer to Bonferroni-adjusted Mann–Whitney U tests between patient groups (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

The post-hoc pairwise comparisons with Bonferroni adjustment (see Appendix E.2) showed that there was a significant difference between MCI and DEM groups for global (2.87×10^{-2}) and local efficiency (2.33×10^{-2}), while CN did not significantly differ from MCI and DEM on those metrics. Non-linearity was also found for the mean clustering coefficient and mean node degree (see Appendix E.4).

The regional clustering coefficient was analysed in more detail using individual cortical regions within the three patient groups, as shown in Figure 5.8. There is notable heterogeneity among regions. Some temporal and limbic regions, such as the inferior temporal gyrus and parahippocampal gyrus, showed visually increased clustering in the MCI group compared to both CN and DEM subjects, reflecting the overall pattern of non-linearity. However, these regional differences failed to remain significant after FDR correction at the global Kruskal–Wallis level ($p_{\text{FDR}} > 0.05$). Nevertheless, post-hoc tests revealed statistically significant differences between MCI and DEM patients in some regions, such as the cuneus, and lateral occipital cortex, and inferior temporal cortex ($p_{\text{Bonf}} < 0.05$). On the other hand, some frontal and cingulate regions, including the caudal anterior cingulate and medial orbitofrontal cortices, demonstrated lower clustering in the DEM group. Notably, the greatest variations in clustering were observed for the regions included in the temporal, DMN and limbic regions. The full statistics are provided in Appendix E.6.

Furthermore, the inter-regional correlation structure of clustering coefficients was investigated for all 68 brain cortical regions. The correlation is shown in Figure 5.9.

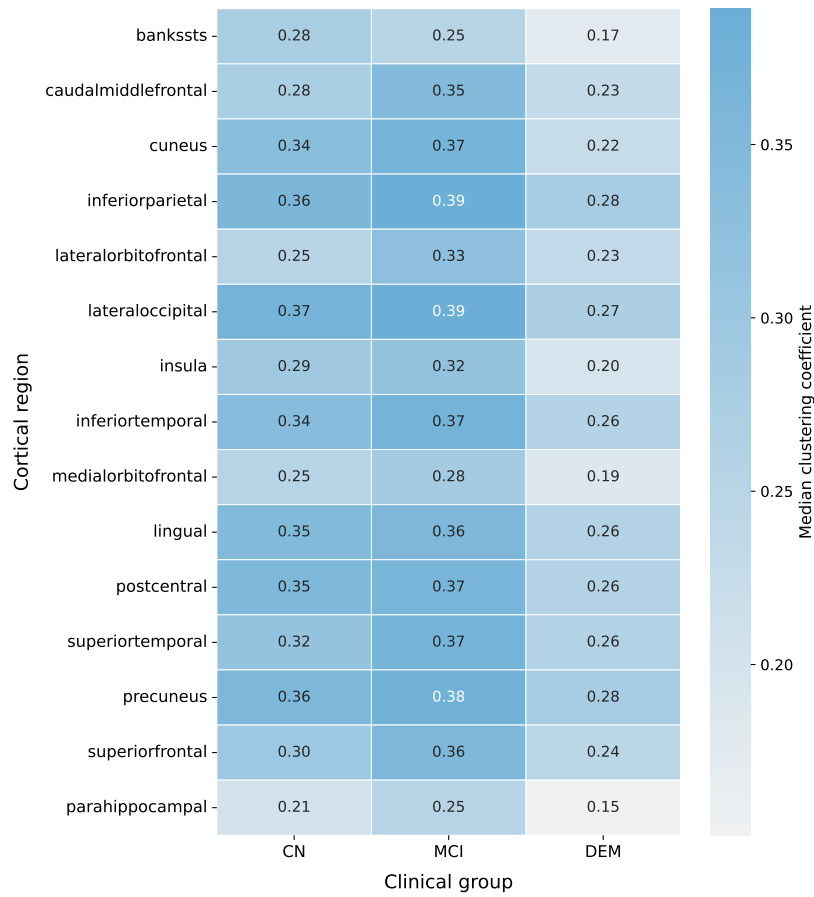


Figure 5.8: Heatmap showing the median values of clustering coefficients for CN, MCI, and DEM groups. Left and right homologous cortical regions were averaged, and the cortical ROIs shown here represent the 15 regions with the lowest FDR-corrected Kruskal-Wallis p -values across the clinical groups. Clustering results for all cortical ROIs are included in Appendix E.5.

Strong correlations are found between regions belonging to similar functional systems. Correlation blocks are visible in the temporal, limbic, and association cortices.

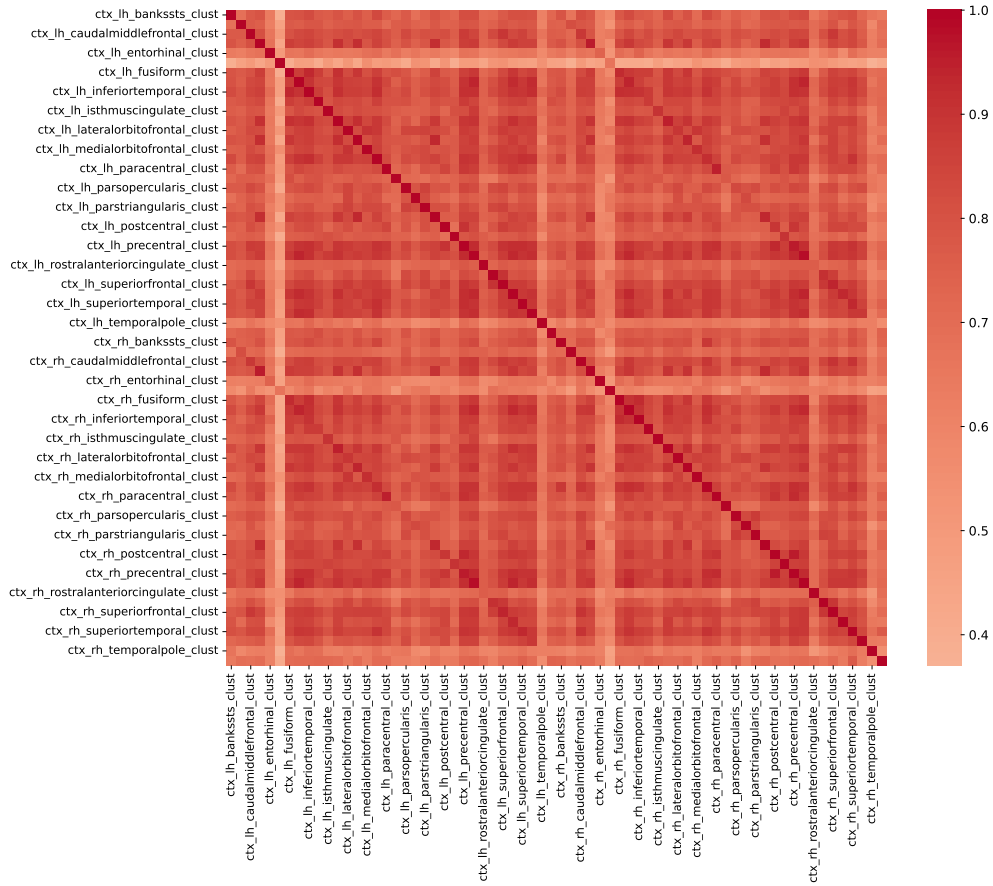


Figure 5.9: *Correlation matrix heatmap of regional clustering coefficients across cortical ROIs, with darker red colours indicating stronger positive associations.*

Further analysis using hierarchical clustering also revealed four major regional clusters showing similar clustering coefficient organisation characteristics (Table 5.2). They include: a medial temporal cluster made up of entorhinal and temporal pole areas; a large associative cluster including temporo-parietal and DMN areas; a frontal/cingulate cluster related to executive and orbitofrontal areas; and a singleton frontal pole cluster.

Table 5.2: *The functional groups were obtained based on hierarchical clustering of the regional clustering coefficient. The complete list of regions classified to each cluster is shown in Appendix E.7.*

Cluster	Main regions	Associated brain function
Medial temporal cluster	Entorhinal cortex, temporal pole	Regions associated with early tau accumulation and medial temporal vulnerability in AD
Frontal pole cluster	Frontal pole	Isolated frontal region exhibiting a distinct clustering profile
Association cluster	Precuneus, inferior parietal cortex, fusiform gyrus, inferior temporal cortex, posterior cingulate cortex, occipital regions	Large associative cluster involving temporo-parietal, occipital, and DMN related regions
Frontal / cingulate cluster	Anterior cingulate cortices, orbitofrontal cortices, superior frontal cortex	Frontal executive and cingulate-related regions associated with cognitive control and orbitofrontal processing

5.4 Relationship between global tau burden and FC

After analysing tau aggregation and FC separately based on clinical groups, the following step involved assessing how regional tau load is directly related to graph theoretical measures of FC, both at the global and regional scales.

5.4.1 Influence of demographic covariates on FC

Before proceeding to assess the association between tau levels and FC measures, the effect of possible covariates on connectivity parameters was investigated. No significant correlation could be detected between age and sex and any of the graph parameters (age: E_g $r = 0.084$, $p = 0.386$; E_l $r = 0.080$, $p = 0.406$; clustering $r = 0.050$, $p = 0.605$; degree $r = 0.065$, $p = 0.505$; sex: all $p > 0.34$). In contrast, educational level correlated significantly with all four connectivity measures (E_g : $r = 0.249$, $p = 1.20 \times 10^{-2}$; E_l : $r = 0.259$, $p = 9.04 \times 10^{-3}$; clustering: $r = 0.234$, $p = 1.83 \times 10^{-2}$; degree: $r = 0.239$, $p = 1.60 \times 10^{-2}$), meaning that more highly educated subjects demonstrate higher global and local network integration.

The cognitive performance of the subjects was further assessed in terms of their global and local network efficiencies using MMSE scores (Figure 5.10).

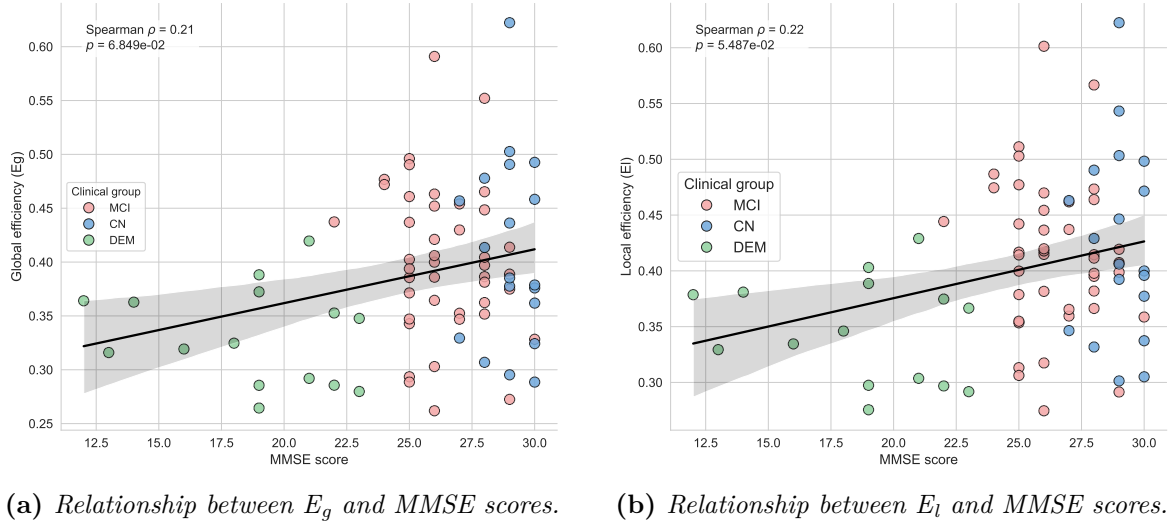


Figure 5.10: Relationships between MMSE and E_g and E_l among subjects. Each dot corresponds to one individual subject, while different colours indicate different clinical groups. MMSE was found to be slightly positively correlated with both E_g and E_l .

Spearman correlation tests showed that there is a weak positive association between MMSE scores and both E_g and E_l , although neither reaching statistical significance ($p > 0.05$). It was noted that the correlation was slightly stronger for E_l .

5.4.2 Association between tau burden and FC

To explore the influence of potential confounders on measures of FC, multiple linear regression models were run using global tau burden, age, sex, and number of years of education as predictors of the four main graph metrics (Table 5.3).

Table 5.3: Multiple linear regression models controlled for age, gender, and education level. $p < 0.05$ are shown in mauve, green indicates $p < 0.01$.

Metric	Tau	Age	Education	Sex	Model statistics
E_g	$\beta = -0.013$ $p = 0.271$	$\beta = 0.001$ $p = 0.078$	$\beta = 0.005$ $p = 0.003$	$p = 0.023$	$R^2 = 0.13$ $p = 3.93 \times 10^{-3}$
E_l	$\beta = -0.014$ $p = 0.223$	$\beta = 0.001$ $p = 0.083$	$\beta = 0.005$ $p = 0.003$	$p = 0.029$	$R^2 = 0.14$ $p = 3.68 \times 10^{-3}$
Mean clustering coefficient	$\beta = -0.014$ $p = 0.457$	$\beta = 0.001$ $p = 0.348$	$\beta = 0.007$ $p = 0.010$	$p = 0.041$	$R^2 = 0.09$ $p = 3.24 \times 10^{-2}$
Mean node degree	$\beta = -0.766$ $p = 0.460$	$\beta = 0.101$ $p = 0.135$	$\beta = 0.493$ $p = 0.003$	$p = 0.022$	$R^2 = 0.12$ $p = 6.89 \times 10^{-3}$

While there were significant regressions for all connectivity measures, none of the

connectivity measures were independently associated with global tau burden. However, years of education were significantly ($p \leq 0.01$) associated with all graph metrics. Additionally, sex was significantly associated with all connectivity measures with women showing higher clustering coefficient values, while age had no significant effect on any model.

Spearman correlation was used to examine the relationship between the mean tau SUVR and four graph metrics at the global level, as illustrated in Figure 5.11. All four graph measures had weak negative relationships with the global burden of tau pathology. None of these were statistically significant.

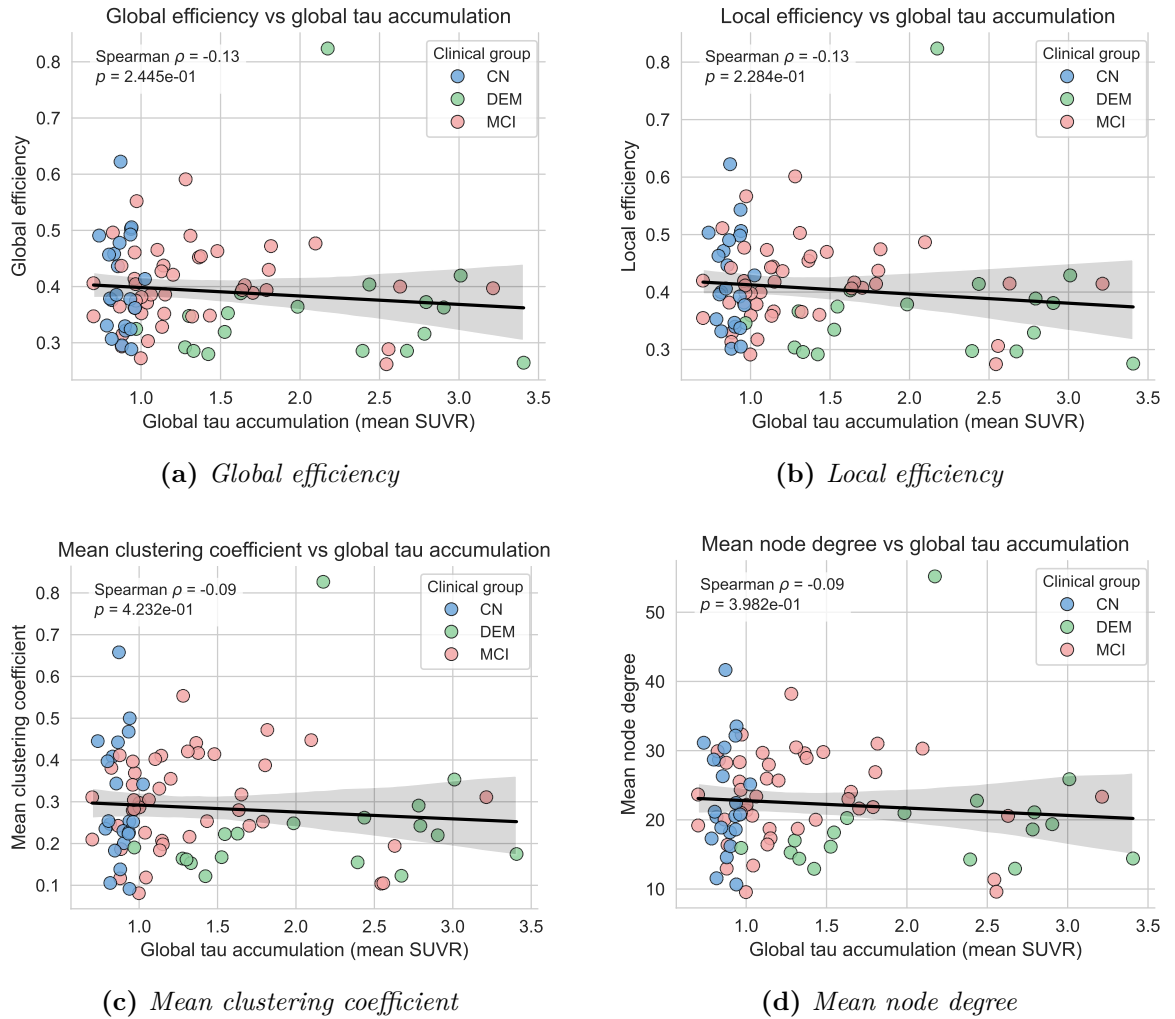


Figure 5.11: Relationship between global tau burden and graph metrics at the global level. Scatter plots illustrate the association between tau SUVR and (a) global efficiency (E_g), (b) local efficiency (E_l), (c) mean clustering coefficient, and (d) mean node degree across participants. The black line represents the overall linear trend across all subjects, independently of clinical group.

While there was some overlap between clinical groups, the distribution across subject-level global tau burden groups maintained a gradient according to their corresponding

clinical group (see Table 5.4).

Table 5.4: *Distribution of clinical groups across global tau burden groups. Subjects were divided into tertiles according to their global tau burden, calculated as the average cortical tau SUVR across all available cortical regions. These groups therefore represent low, intermediate, and high global tau burden at the subject level.*

Global tau burden group	CN (%)	MCI (%)	DEM (%)
Low global tau burden	90.4	9.6	0.0
Intermediate global tau burden	68.5	27.8	3.7
High global tau burden	3.3	60.0	36.7

In the low global tau burden group, the majority of the subjects belonged to the CN group (>90%), while the intermediate global tau burden group, even though remaining mostly composed of CN subjects, included a larger proportion of MCI subjects (> 27%). In the high global tau burden group, most of the subjects belonged to the MCI group, followed by DEM subjects.

In order to address possible heterogeneity, the association between tau burden and connectivity was also analysed separately for the early, intermediate, and late stages of tau pathology, as shown in Table 5.5.

Table 5.5: *Spearman correlations between stage-specific tau burden and global graph metrics. The regions of each tau stage are described in section 4.4.3.*

Tau stage	Graph metric	Spearman correlation	FDR-corrected p-value
Early tau	E_g	$\rho = -0.103, p = 0.265$	0.448
	E_l	$\rho = -0.110, p = 0.230$	0.448
	Mean node degree	$\rho = -0.080, p = 0.385$	0.448
	Mean clustering coefficient	$\rho = -0.070, p = 0.448$	0.448
Intermediate tau	E_g	$\rho = -0.163, p = 7.61 \times 10^{-2}$	0.448
	E_l	$\rho = -0.169, p = 6.43 \times 10^{-2}$	0.448
	Mean node degree	$\rho = -0.140, p = 0.129$	0.448
	Mean clustering coefficient	$\rho = -0.132, p = 0.151$	0.448
Late tau	E_g	$\rho = -0.095, p = 0.304$	0.448
	E_l	$\rho = -0.101, p = 0.271$	0.448
	Mean node degree	$\rho = -0.082, p = 0.376$	0.448
	Mean clustering coefficient	$\rho = -0.075, p = 0.413$	0.448

For the four graph measurements and the three stage-specific tau burden measures, all associations remained weak and negative. Out of the four graph measures, none showed significant association.

5.5 Tau-connectivity similarity and network organisation

With the lack of evidence for a linear association between global tau burden and connectivity measures, we tested whether the spatial organisation of tau deposition might be associated with functional brain network structure.

The pairwise FC (averaged across subjects) was plotted against the pairwise tau similarity, as illustrated in Figure 5.12.

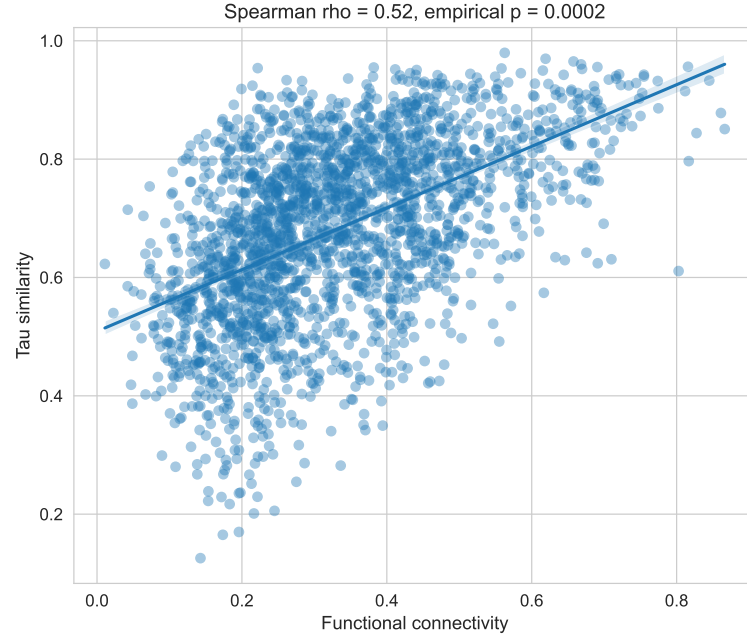


Figure 5.12: *FC versus Tau similarity between cortical regions. One point represents one pair of regions. FC was obtained by averaging across subjects, whereas tau similarity was calculated using the correlation between the tau SUVrs of each region.*

A robust positive association was found for all region pairs: those that displayed greater FC had more similar tau buildup patterns. Significance testing was conducted through a permutation test using region label randomisation, showing that the relationship was not likely to occur by chance ($\rho = 0.52$, empirical p-value = 0.0002).

The robustness of the association between tau similarity and FC was also assessed at the different clinical stages of the disease, as shown in Figure 5.13. The Spearman correlation between FC and tau similarity was higher with advancing disease stages: $\rho = 0.32$ for CN, $\rho = 0.43$ for MCI, and $\rho = 0.50$ for DEM. Significance was again confirmed using a permutation test based on shuffling the region labels, with significant empirical p-values observed for all clinical groups ($p = 0.0002$).

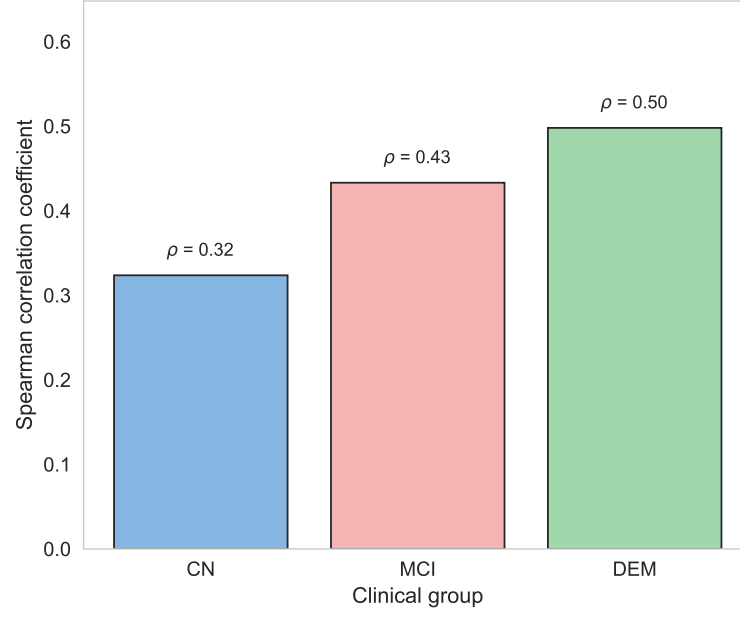


Figure 5.13: *Spearman correlation between FC and tau similarity stratified by clinical groups.*

For each of the major RSNs considered individually, there was variability regarding the connectivity-tau similarity association, as presented in Figure 5.14.

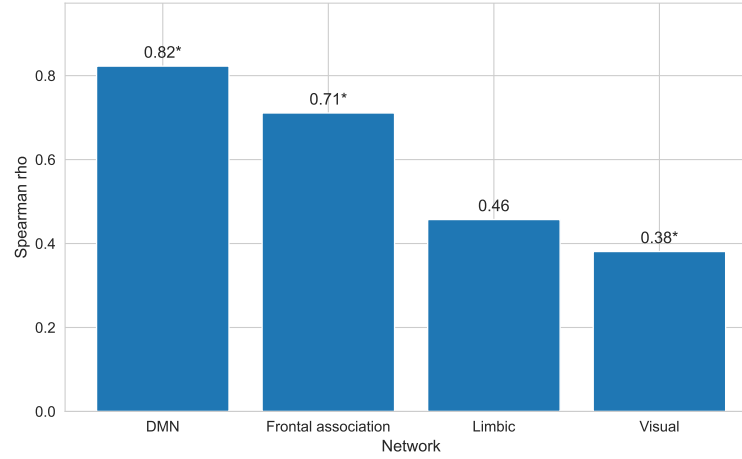


Figure 5.14: *Association between FC and tau similarity across important RSNs. The correlation between FC and tau similarity was determined using Spearman correlation coefficient within each network. The asterisks indicate significant correlations using a permutation test ($p < 0.05$). Statistical details are listed in Appendix F.1.*

More particularly, the connectivity-tau similarity association was the highest for the DMN ($\rho = 0.82$), followed by the frontal ($\rho = 0.71$), limbic ($\rho = 0.46$), and visual ($\rho = 0.38$) networks.

5.6 Seed-based analysis and prediction of regional tau burden

To evaluate whether the FC pattern of a cortical region can predict the tau burden map, a seed-based correlation analysis was first carried out on all 68 cortical regions to find the best seeds.

As illustrated in Figure 5.15, the entorhinal cortex (for both hemispheres) showed the highest Spearman correlation for both CN and MCI groups, while inferior temporal cortex showed the highest correlation for DEM. The ten seeds showed statistical significance for all three groups after FDR adjustment ($p < 0.01$). The fusiform and parahippocampal cortices also showed highly correlated results ($\rho = 0.44$ - 0.62). The lingual cortex was also found to be one of the top seeds by mean ρ value in groups.

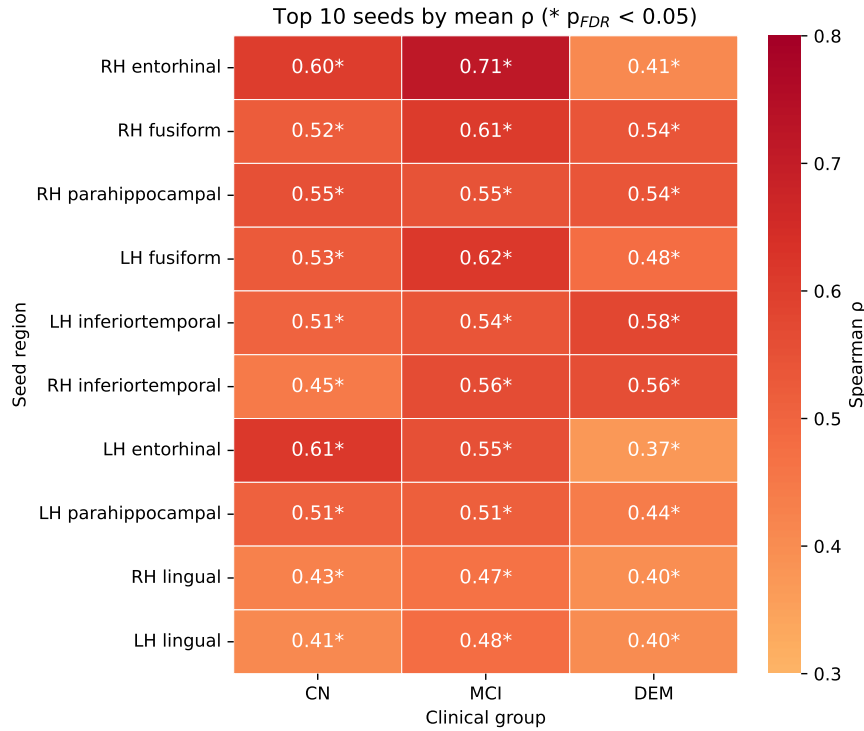


Figure 5.15: Seed-based associations between FC profiles and regional tau pathology across clinical groups. Correlation analysis was done using Spearman correlation coefficients between the connectivity pattern of each seed and the regional tau burden, based on group average connectivity matrices.

As shown in Figure 5.16, anatomical distance was able to explain almost no variance of regional tau burden at all ($R^2 = 0.004$), whereas FC was able to explain a considerable amount ($R^2 = 0.48$). The addition of anatomical distance to the model resulted in a slight increase in variance explained by the model ($R^2 = 0.52$).

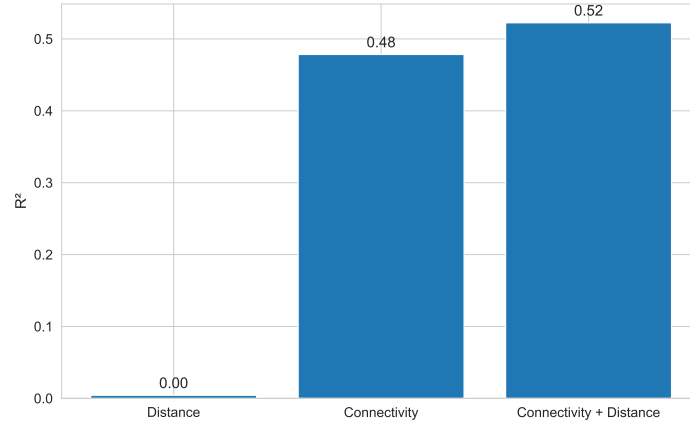


Figure 5.16: A comparison between linear regression models that utilize seed regions for prediction of regional tau burden in relation to either anatomical distance, FC, or both of these variables together, in which the seed region is the left entorhinal cortex.

As can be seen from Figure 5.17, the individual distribution of coefficients of determination (R^2) was strongly skewed toward low values, with a median R^2 of 0.026, as opposed to a much larger group-wise value of $R^2 = 0.459$. Individual Spearman correlations were quite variable, with a median $\rho = 0.163$.

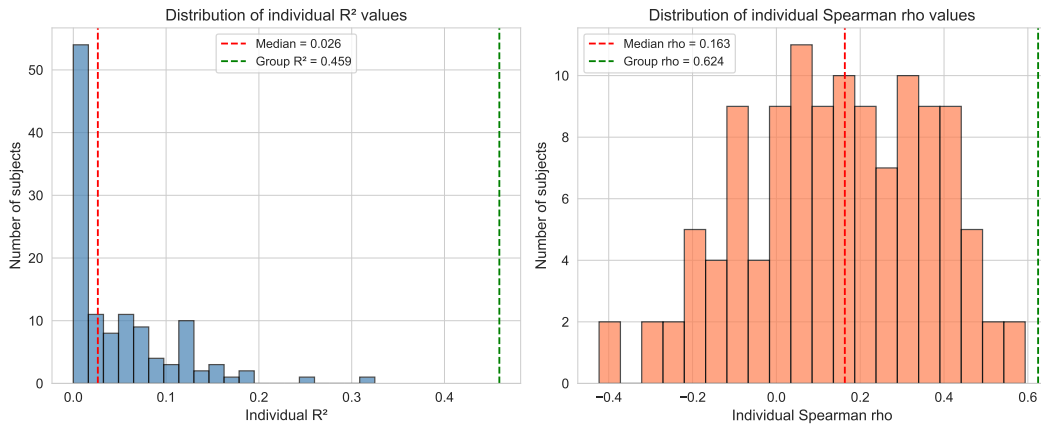


Figure 5.17: Subject-specific relationship between seed-based FC and regional tau deposition, with reference to the left entorhinal cortex. Left: distribution of individual coefficients of determination (R^2) obtained via linear regression analysis between connectivity and tau deposition in cortical targets. The red dotted line represents the median individual (R^2), whereas the green dotted line represents the group (R^2). Right: distribution of individual Spearman correlations between connectivity and tau deposition in participants.

5.7 Tau staging and longitudinal accumulation

In this part, an attempt is made to describe tau deposition in early, middle, and late Braak stages first based on a cross-sectional approach before examining the actual

longitudinal alteration in tau load among participants who had undergone repeated PET scanning.

Median tau SUVR values were independently determined for early, intermediate, and late-stage regions within each of the three clinical groups, as shown in Figure 5.18. For CN subjects, tau SUVR values were consistently low at all three stages of progression (median SUVR between 0.83 and 0.93). In patients with MCI, median tau SUVR values were high in both early and intermediate stage regions (median SUVR = 1.86 and 1.65, respectively) while they were relatively low in late-stage regions (median SUVR = 1.11). In DEM cases, the highest level of tau pathology occurred in intermediate stage regions (median SUVR = 3.10) followed by late-stage regions (median SUVR = 2.36) and early-stage regions (median SUVR = 2.28).

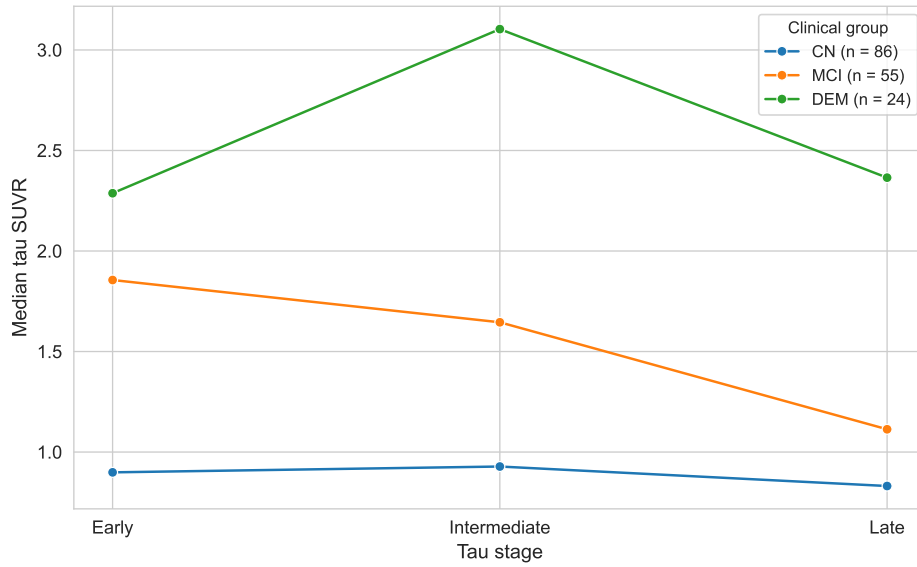


Figure 5.18: *The median tau SUVR values for the early, intermediate, and late Braak-like stages among the CN, MCI, and DEM subjects.*

The complete SUVR values for tau in all the groups and at different tau stages are provided in Appendix D.3.

To measure the within-group variability in the deposition of tau, the standard deviation (SD) of the tau SUVR was calculated for all the clinical groups as well as the different tau stages, as shown in Figure 5.19. Low SD values were observed for the CN group at all stages (SD < 0.30). On the contrary, a numerically higher variability was observed in the MCI and DEM groups, especially for intermediate and late stages (with an SD value up to 1.17 in the DEM group for intermediate regions).

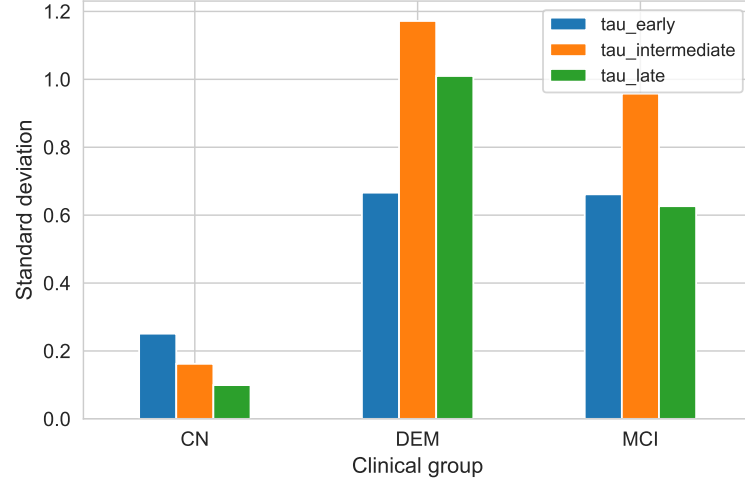


Figure 5.19: Standard deviation of tau SUVR in early, intermediate, and late tau stages for each clinical group.

No correlation could be established between age and tau burden at the cohort level (Spearman $\rho = 0.087$, $p = 0.264$). However, on a group-level analysis, a negative association was observed for the DEM group ($\rho = -0.545$, $p = 5.94 \times 10^{-3}$). The corresponding plot is visible in Appendix F.2.

Lastly, the rate of longitudinal tau build-up was assessed for subjects with repeated PET acquisitions, as shown in Figure 5.20. The annualised mean increase in global tau SUVR was five times greater in the MCI cohort (mean annualised $\Delta = 0.045$ SUVR/year) than in the CN cohort ($\Delta = 0.009$ SUVR/year). Longitudinal data from the DEM cohort were not sufficient to estimate tau change reliably.

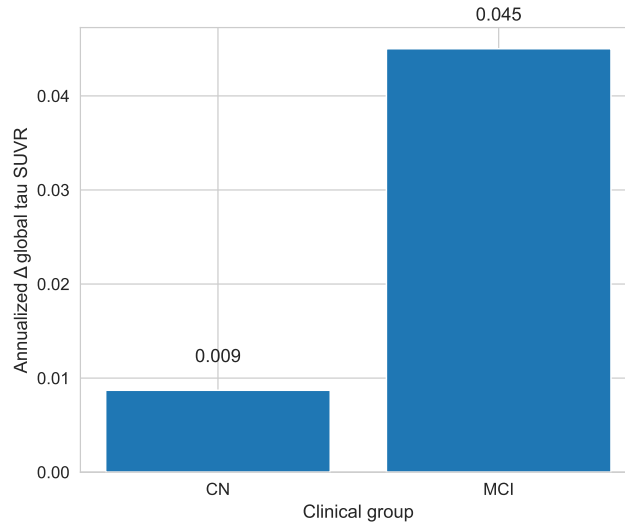


Figure 5.20: Mean annualised longitudinal change in global cortical tau SUVR by clinical group. Δ tau was calculated as the difference between the last and first available session per subject, divided by the time interval between both scans in years.

Chapter 6

Discussion

6.1 Tau propagation and functional brain networks

The increase in tau protein was most noticeable in the medial temporal areas (Figures 5.1, 5.2, 5.3), especially the entorhinal cortex, the parahippocampal gyrus, the inferior temporal cortex, and the fusiform gyrus, which is expected based on the susceptibility of these areas to neurodegeneration in AD and roughly coincides with Braak stages I-IV. Notably, while there were significant differences between CN and MCI for all four regions, the entorhinal cortex did not show significant differences between MCI and DEM after Bonferroni correction (Figure 5.2). It appears that the accumulation of tau in this brain region starts to plateau at the MCI stage before spreading to adjacent areas. Notably, it is important to mention that the involvement of lateral occipital and caudal middle frontal regions, which exhibit particularly high tau SUVR values, should be interpreted carefully. These brain areas are usually not considered early-affected regions based on Braak stages, and the high SUVR values observed in these areas can be attributed to the non-specific binding of [18F]MK-6240 tracer or partial volume effect. Thus, it is critical to consider regional measurements of tau PET in the light of the characteristics of the tracer itself and neuropathology-related priors.

Additional analysis using cross-sectional staging with tau SUVR revealed that the CN group exhibited consistently low tau SUVR in all regions, indicating a homogeneous and relatively preserved distribution of tau at this stage. On the other hand, MCI exhibited increased tau burden in regions from early and intermediate stages within the temporal lobe. For the DEM group, an increased tau burden was noted in intermediate regions, which may indicate that tau had begun to spread throughout the neocortex.

The longitudinal tau PET data provided additional evidence to support these findings. The annualized mean increase in global tau SUVR was five times greater in the MCI

cohort (mean annualized $\Delta = 0.045$ SUVR/year) than in the CN cohort (mean annualized $\Delta = 0.009$ SUVR/year), suggesting increased rates of tau deposition after developing cognitive decline. This pattern aligns with the findings from previous analyses showing increased tau coupling in the MCI cohort (Figures 5.13, 5.15).

Beyond this regional progression, one of the central results from this study is the significant association between brain FC and the distribution of tau pathology within the cerebral cortex. In fact, this correlation became more pronounced with the progression of the disease (Figures 5.12, 5.13), consistent with the theory of a network-based model of tau propagation in AD.

Hypothesis on the spread of tau pathology among synaptically connected neural circuits has been supported by a growing body of experimental and clinical evidence [10, 11, 20, 21]. At the cellular level, studies have revealed that tau proteins tend to be released at synaptic terminals and are then absorbed by connected neurons. This implies a prion-like trans-synaptic transmission mechanism that is more dependent upon the architecture of brain networks rather than anatomical adjacency between cells alone [11]. The present study extends this hypothesis to the large-scale functional network level, showing that the spatial distribution of tau across the cortex closely mirrors the organisation of functional RSNs.

It is important to note that FC explained 48% of the variance in the regional tau distribution (Figure 5.16). This conclusion coincides with the results obtained by Vogel et al. (2020) [11] using an ESM. The authors were able to show that as much as 70% of the variation in the pattern of tau transmission can be explained by functional connections between brain regions. Also, similar conclusions were drawn by Nabizadeh (2024) [21]. According to the author, the rate of tau accumulation in non-epicentre regions decreases as their FC with tau epicentres declines. Connectivity-based distance from tau epicentres is then considered a strong predictor of local tau accumulation rates. The current research adds to this literature by showing, not only that connectivity is predictive of tau deposition, but also that this relationship becomes increasingly predictive from normal cognition to Alzheimer’s DEM (Figure 5.13).

The progressive enhancement of the connectivity–tau coupling from CN to MCI and DEM needs special consideration. In healthy subjects, tau protein deposition remains relatively localised to medial temporal regions and is possibly only in its early phase of spreading throughout the neural network, hence the poor association between network structure and tau deposition. However, with progression of the disease, tau spreads into highly connected cortical structures, leading to increased correspondence between the tau deposition pattern and the underlying network structure, thereby generating better coupling scores. The gradual strengthening of the tau-connectivity coupling across

disease stages supports the hypothesis that network-based propagation mechanisms play an increasing role as tau spreads beyond the initial medial temporal epicentres. However, this correlation refers to the network level as a whole, and therefore does not necessarily hold for all pairs of regions.

Nevertheless, the current results have yet to establish the directionality of the association between tau pathology and connectivity. Although the observations support the theory that functional brain networks facilitate tau propagation, it should be noted that progressive tau accumulation itself might also cause changes in the brain's FC pattern, thus leading to the observed coupling. The two theories are not mutually exclusive and could interact dynamically over the course of AD. Further longitudinal studies are needed to determine the causality underlying the association between tau spreading and changes in functional networks.

In addition, the results of seed-based analysis furthered this characterisation by indicating that the entorhinal cortex was the most informative seed for predicting tau distribution across the brain overall (for CN and MCI), followed by the fusiform gyrus, the parahippocampal gyrus, and the inferior temporal cortex that showed the highest correlation in the DEM group (Figure 5.15). The order in which these areas were listed is very close to the typical progression of tau pathology as seen in AD, with the entorhinal cortex being the primary tau epicentre from which pathology spreads to connected temporal and eventually parietal and frontal regions [10, 11]. This is in line with the Braak hierarchical network spreading model [8]. The particularly strong relationship between tau burden and connectivity in the DMN (Figure 5.14) suggests that the way the DMN is organized functionally is likely to facilitate network-dependent propagation of the protein. The hypothesis is supported by the fact that hub areas, defined as having a high node degree, had a much greater tau burden than other parts of the brain (Figures 5.4, 5.5), suggesting that the risk of tau build-up is especially pronounced for highly interconnected nodes due to their greater exposure to tau spreading routes.

As a whole, these results provide multimodal evidence in support of the network-based propagation model of tauopathy in AD, suggesting that resting-state FC may provide a useful framework for studying tau distribution across the cortex.

6.2 Alterations of FC across disease stages

In the graph theoretical analyses performed in this study, a consistent group-level pattern trend in the functional network organisation across clinical stages has been revealed. This involves the tendency of greater functional network efficiency and connectivity in patients with MCI compared to CN subjects before declining to a lower level in patients with DEM (Figure 5.7). However, while the results from Kruskal-Wallis

analyses showed that there were statistically significant differences among the groups concerning E_g and E_l (Figure 5.7), none of the post-hoc pairwise comparisons using Bonferroni correction were statistically significant except the comparison between the MCI group and the DEM group (Section 5.3). This may indicate that this group-level pattern can be statistically supported at the global level despite the difficulty in proving the significance of pairwise comparisons likely due to small sample size and large inter-individual variance.

The $CN < MCI > DEM$ pattern fits the theory of compensatory hyperconnectivity at the early stages of AD, a concept that has been observed in previous studies using rs-fMRI [15, 16]. Based on this theory, the brain reacts to the early pathophysiological changes like synaptic dysfunction, tau build-up, and neurodegeneration by temporarily increasing FC, thus maintaining cognition despite the pathological changes.

This theory finds support from the research conducted by Schultz et al. (2017), who found that $A\beta$ and tau deposition in healthy subjects triggers successive phases of hyperconnectivity and hypoconnectivity in some brain networks, such as default mode and salience networks [15]. It is important to mention that the presence of higher E_g and E_l among MCI patients in comparison with CN and DEM patients is in line with this theory because MCI represents an intermediate state where the compensatory effect continues before network dysfunction occurs. It should, however, be noted that the above interpretation needs to be considered along with a different interpretation. The higher level of connectivity found among the MCI subjects can be interpreted through the concept of compensatory hyperconnectivity. However, this interpretation should be treated with caution, since rs-fMRI results may be influenced by disease stage heterogeneity within the MCI group, including the duration of the MCI stage and the proximity to conversion to dementia. It is worth noting that due to the mostly cross-sectional nature of the data available, it is not possible to test this hypothesis within this study.

The further drop of all the connectivity measures in the group of patients with DEM (Figure 5.7) shows that this adaptive process seems to fail due to the spread of tau beyond medial temporal regions to involve large portions of the neocortex. In other words, at this stage, the pronounced synaptic loss and neurodegenerative processes associated with the presence of a significant amount of tau might be progressively obstructing the ability of the brain to adapt, leading to a degradation of the network structure. The deterioration of network efficiency found among patients with DEM is consistent with the known functional disconnection found in cases of late-stage AD in the DMN [14] and in general is part of the concept of Alzheimer's as a disconnective disorder.

However, another non-exclusive explanation needs to be pointed out. Functional hyperconnectivity identified in the MCI stage may partially indicate hyperactivity induced by pathological impairment of homeostatic regulation processes. In fact, hyperactivation was found to occur in brain structures prone to early deposition of pathogenic tau protein, like the hippocampus and precuneus, suggesting this phenomenon may be pathobiologically detrimental and even a factor promoting disease progression [52]. On the other hand, hyperactivity found in regions without significant pathology, such as the frontal lobe, seems to fit better within the framework of compensatory hyperactivation. Thus, the biological significance of hyperconnectivity might differ according to brain area and disease stage, and future longitudinal investigations will help understand the underlying processes better.

Further elaboration on these results was made possible through the regional clustering analysis, which revealed differences in connectivity changes in different regions of the cortex. Several temporal and limbic regions showed the highest clustering increases among patients with MCI, while some cingulate and frontal regions showed decreases in clustering at various disease stages (Figure 5.8). Such increased clustering could be associated with local compensatory activity due to early synaptic dysfunction in these regions. By contrast, the lower connectivity levels found in the frontal and cingulate regions could reflect secondary disconnection effects induced by tau pathology in adjacent temporal regions.

However, it is worth acknowledging that the absence of statistical significance for some comparisons limits the conclusions that can be made based on the results obtained. First of all, relatively modest numbers of subjects were analysed in each clinical cohort along with considerable individual differences in the connectivity, probably limiting statistical power, preventing the discovery of significant differences between these groups. At the same time, consistency with other biological coherence and theoretical assumptions allows us to conclude that the pattern identified may reflect actual changes caused by AD.

Most importantly, while no significant changes were found at the global level, regional-level studies revealed some local connectivity changes, particularly in the temporal and limbic areas that have shown vulnerability to AD. This means that changes in connectivity could first happen within specific brain networks before occurring globally.

6.3 Local versus global effects of tau pathology

Another finding in this work was the lack of a strong correlation between tau burden and any of the four graph metrics (global efficiency, local efficiency, clustering coefficient, and node degree) when corrected for demographic variables. In fact, the results of the

multiple linear regression model adjusting for age, sex, and education indicated that global tau burden was not a significant predictor of connectivity measures ($p > 0.22$ in all cases, see Table 5.3), even though the overall models remained significant, driven primarily by education. These results support previous studies that had suggested that global scalar measurements of tau burden may not be enough to understand the spatially distributed nature of tau's influence on functional networks and that a network-level analysis would thus be more sensitive than averaging regional metrics [11, 20].

The seeming contradiction between the existence of high levels of association between tau and connectivity on a network-level scale (Section 5.5), while simultaneously observing very low associations on an individual metric level, can be explained through an understanding of the distributed characteristics of tau pathology within the brain. This is because it not only has a regional effect upon the connectivity of particular brain areas, but may rather alter the spatial organisation of functional networks more globally. In such a scenario, tau affects how connected different brain regions are with each other, instead of affecting connectivity in one particular region. This concept of local versus network-based changes is important to understand the neuroimaging results associated with AD because looking at only one brain region or one measure of connectivity might not be enough.

This interpretation is backed up by the results of Sintini et al. [20], who have shown that functional network analysis performed through the use of rs-fMRI often makes it difficult to establish the role played by the propagation of tau versus other pathological factors, like cerebral atrophy or microvascular problems, at the regional level. The current findings contribute to this evidence by proposing that global patterns of tau distribution, rather than the regional concentration of tau pathology, may be important for understanding FC alterations associated with tau burden. Indeed, this idea fits the ESM framework put forward by Vogel et al. (2020) [11], where it was shown that tau diffusion follows global connectivity patterns better than local structural properties of individual regions.

Additionally, as seen in the results, there was a clear gradient of tau SUVR values with increasing node degrees for different brain areas (Figures 5.4, 5.5). This could imply that hub nodes may be especially vulnerable due not only to their intrinsic characteristics but also to their position in the network. As shown in Table 5.5, the regional tau burden of the intermediate Braak-like stage showed consistently stronger (though non-significant) negative correlation with connectivity metrics compared to the early and late stages, maybe suggesting that tau accumulation is more linked to network alterations within intermediate-stage regions.

Moreover, the fact that tau deposition is more alike in pairs of regions that are connected

functionally (Figure 5.12) may support the idea that tau deposits seem to spread based on network structure rather than a process of mere local transmission. The ability of FC to predict regional tau deposition over anatomical proximity (Figure 5.16) lends statistical significance to the latter explanation, indicating that network-based studies might hold more importance than only regional investigations into the mechanism of tau spreading.

This heterogeneity was illustrated by subject-level seed correlations, which revealed a strong bias towards lower R^2 scores for subjects (median $R^2 = 0.026$), in contrast to the group-level R^2 value of 0.459 (Figure 5.17). Similarly, the individual-level Spearman correlations display significant variations with a median value of $\rho = 0.163$. The difference between the two levels of correlation demonstrates that, while the relationship between connectivity and tau is strong and reliable on a population level, it does not necessarily hold for each individual, maybe reflecting inter-individual differences in disease stage, tau spreading trajectory, or compensatory mechanisms.

All considered, these results indicate that the impact of tau pathophysiology in AD may be best characterised by network organisation at a larger scale than by region-by-region or measure-by-measure analyses. This could have implications for biomarker identification and targeted treatment approaches, as it implies that the targeting of interventions designed to prevent tau propagation should eventually focus on network organisation rather than localised brain regions.

6.4 Influence of covariates and cognitive reserve

Among the demographic covariates considered for this analysis, only education and sex proved to be significant factors (Table 5.3) in predicting the values of the connectivity metrics. Education correlated positively with E_g , E_l , mean clustering coefficient, and mean node degree (Table 5.3).

Educational level is frequently regarded as an indicator of cognitive reserve, defined as the ability of the brain to maintain its cognitive performance in spite of the presence of neuropathological lesions. The correlation found between education years and the graph metrics implies that people with a larger cognitive reserve are able to preserve more functional network organisation in the presence of tau.

In addition, there was a slight positive association between MMSE scores and both E_g and E_l (Figure 5.10). This suggests that participants who performed poorly on the cognitive task also displayed poor network integration and segregation. While these associations were not statistically significant, the fact that the trend was consistent in both measures implies a link between functional efficiency and cognitive function.

This interpretation is consistent with a large number of studies that have found that cognitive reserve affects the link between neuropathological load and the clinical manifestation of AD. Increased cognitive reserve has been linked with preserved FC in the DMN despite considerable accumulation of amyloid and tau, and may help explain why some individuals have later onset of cognitive decline compared to neuropathological load [53–55]. The current results extend these observations to the level of whole-brain graph theory metrics, showing how the effect of cognitive reserve can be seen even on a larger scale than in specific brain networks.

The lack of clear age effects on connectivity measures is worth highlighting, considering the known effect of age on the alteration of functional brain connectivity in the general neuroimaging research field [56]. Perhaps the reason lies in the rather narrow age spectrum of patients who belonged mostly to the elderly patient population usually linked to AD. On the other hand, one can argue that within an AD population, the induced changes in connectivity override the usual effects of age on connectivity and thus, the former effect is easier to detect. This hypothesis is further supported by the observed results, which demonstrate a stronger association between patients’ clinical group and connectivity measures than between connectivity and age (Table 5.3, Section 5.4).

Sex emerged as a significant factor in predicting all four connectivity metrics in our analysis, with women showing higher connectivity values than men. However, the result must be interpreted with caution, since the cohort is unbalanced in terms of gender composition (56.8% female). This could very well indicate the existence of a selection bias in our data, although there are studies supporting the notion of increased FC in females, especially in the DMN [57].

6.5 Limitations

However, despite all the strengths of the multimodal methodology used in this research, there are certain limitations that should be considered while analysing the results presented in the previous sections.

The first important limitation concerns the temporal match between the PET and fMRI scans. In the methodology section, it was explained how PET and fMRI sessions were matched such that there would be no more than 371 days between them. The limitation of this approach is that the accumulation of tau protein is an ongoing process, which is evident from the results obtained in section 5.7. For instance, the MCI group has a mean accumulation rate of $\Delta = 0.045$ SUVR/year. Therefore, conducting the fMRI scans after a period of up to twelve months might introduce some variability in the analysis of the relationship between the burden of tau and FC metrics, and may not

accurately capture the functional networks at the time of the PET scan.

The second limitation relates to the representativeness of the dataset. The selection criteria could have affected the generalisation of the findings obtained and induced selection bias since the patients in the current dataset may differ from the patients without such data in disease severity, follow-up opportunities, motion, or other factors, hence limiting the generalisability of the findings to the broader AD population.

The third limitation is related to the number of subjects in some of the analyses that were conducted in this study. Although having a relatively large cohort provides reasonable statistical power for cross-sectional group comparisons, the number of subjects with matched PET and fMRI data was rather limited. This limitation probably explains why there was no statistically significant difference among clinical groups in some of the comparisons of the graph theoretical measures since the high variability in connectivity among the members of each group, particularly MCI and DEM, requires a larger number of subjects to detect even moderate effects. Another important point is the absence of longitudinal fMRI data in the majority of subjects, which would enable researchers to test how the co-evolution of tau accumulation and connectivity occurs in individual patients.

Furthermore, there is an unequal distribution of participants among clinical groups, with fewer DEM participants than CN and MCI participants. The reason behind such an uneven distribution could be related to the practical issue involved in collecting multimodal PET and rs-fMRI in patients who belong to a more advanced clinical stage. In fact, it is harder to collect good-quality data from patients in a more advanced stage because of movement, increased disease severity, and lower availability for follow-ups. Therefore, findings regarding the DEM group should be treated carefully.

Another limitation refers to the cross-sectional nature of most studies discussed in this work. Although cross-sectional comparisons of clinical groups can offer important information on the disease stage-dependent development of tau pathology and FC, they cannot make any conclusions regarding the causal relationships and direction of these two phenomena in the individual patient. The observed link between FC and the distribution of tau may be due to an effect of connectivity on the spread of tau pathology, a reverse effect of tau pathology on FC, or even a simultaneous effect of some third factor on both of them. A longitudinal study of tau load and connectivity changes would be required in order to properly separate out these options and determine the direction of the relationship between tau and connectivity.

Moreover, there is the issue of methodological decision-making in terms of the processes used in preprocessing and analysis. While the use of fMRIPrep contributes to more standardised and replicable pipelines for analysis, analytical decisions such as the confound

regression approach used, the choice of atlases and how connectivity was estimated may have affected the results. For instance, the use of the 68-regions Desikan-Killiany atlas might have limited the spatial resolution of the analyses, thereby potentially masking more localised effects that could be seen with finer-grained parcellations. Notably, this atlas comprises only cortical regions and does not take into consideration subcortical structures like the hippocampus and amygdala, regions that are clinically significant in AD and have been shown to be involved in the disease progression along with structural alterations [58, 59].

A further limitation refers to the specificity and spatial resolution of the tau PET tracer used in this study. Even though [18F]MK-6240 is a second-generation tracer that has greater specificity than previous tracers, there could be off-target binding that may affect the estimates of the regional tau levels. Moreover, the reconstruction of PET images was performed using point spread function models. But no further correction for partial volumes was done on the obtained SUVr that were taken as measurements in this experiment. This may cause partial volume effects and spillover signals in the neighbouring cortical areas, which may affect the accuracy of SUVr in structures such as the entorhinal cortex.

The last limitation relates to the absence of amyloid PET data in the connectivity analysis. While the literature discussed in this work highlights the crucial role that $A\beta$ and tau pathologies play in altering brain networks and their possible synergy, there were only a limited number of individuals in the current study cohort who had amyloid data. This means that the joint influence of both amyloid and tau accumulation on brain connectivity was not assessed in the current study. Incorporation of both biomarkers in one model will provide a better understanding of the pathological processes underlying AD.

6.6 Future directions

The findings of this study open several promising avenues for future research, both in terms of methodological refinements and broader scientific questions. The limitations identified in the previous section provide a natural starting point for defining priorities for future work, while the results themselves highlight additional perspectives extending beyond the scope of the present study.

The first priority that should be considered is the expansion of longitudinal multimodal analyses. As this study is largely based on cross-sectional methodology, the causality of the association between the propagation of tau protein and changes in FC is difficult to establish. In this respect, future research needs to employ longitudinal multimodal analysis, with the acquisition of both tau PET and rs-fMRI images. Such an approach

would enable researchers to trace the simultaneous evolution of tau protein burden and brain network organisation.

Another interesting direction concerns the combination of complementary imaging modalities and advanced network modelling techniques. In view of the clear relationship between the pathologies of $A\beta$ and tau in AD, future work could benefit from using data on amyloid PET in order to investigate whether the connection between connectivity and tau found in the current study is affected by the amyloid load. The use of structural connectivity based on diffusion MRI data would also facilitate understanding the contribution of both functional and structural brain network organisation to the tau spreading process. The combination of these techniques within advanced tau spreading models, such as ESM or MCA, could help achieve a better mechanistic understanding of tau spreading dynamics.

Further research may also aim to improve the understanding of functional brain networks. While the current study involved analysis using dFC methods, other techniques, such as hidden Markov models and state-transition analysis, may prove more sensitive when looking for changes in brain networks that are linked to diseases. Specifically, connectivity states where the DMN is strongly engaged can be more closely associated with tau pathology and propagation than average connectivity. Likewise, using brain atlases with finer parcellations, such as the Schaefer-200 parcellation [60], may help identify more localised regions of tau pathology and connectivity changes compared to the 68 regions Desikan-Killiany atlas used in the current study. Future work should also explore the role played by subcortical structures such as the hippocampus and amygdala in the FC-tau correlation.

An even more clinically relevant direction would be to explore the possibility of using connectivity-based biomarkers. While rs-fMRI cannot be considered a direct surrogate for tau pathology, it may, however, be a useful tool to predict future tau propagation from tau epicenters and could be envisioned as a tool to identify individuals most at risk of rapid tau propagation and cognitive decline.

Ultimately, there is a need for future research to ensure that larger and more diverse cohorts are included in the study to enhance the validity of the results obtained. This way, the effects of genotypes, gender, and stages of the disease can be assessed by including large cohorts of DEM patients, APOE4 carriers, and more demographic and clinical variations among the sample population.

Conclusion

This study aimed to explore the association between tau pathology and FC in AD through a multimodal analysis approach by integrating the use of tau PET imaging and rs-fMRI.

It was found that there is a progressive increase in tau deposition with stages of clinical disease manifestation, especially in brain regions that were early affected by the disease. Analysis of FC showed non-linear changes with stage progression, with an observed trend of increasing connectivity in intermediate stages followed by a decrease in later stages, implying a possible compensatory mechanism at earlier stages. Another important finding is that there is a significant correlation between FC and the spatial pattern of tau, and that this association appeared to increase with the progression of the disease. These findings are consistent with the hypothesis that tau pathology may spread along functional brain networks, reinforcing the idea that AD is a network-based disorder. More locally, the lack of significant correlations between the burden of tau and the individual graph metrics suggests that local tau accumulation alone may not fully explain connectivity alterations, indicating that the influence of pathology may also need to be evaluated at the network scale rather than at the regional-metric level. Moreover, the impact of education on some connectivity metrics indicates the possible involvement of cognitive reserve in the organisation of brain networks despite the presence of pathology.

Nevertheless, there are some limitations associated with this study. For example, there is a mismatch in the timing of the PET and fMRI imaging that might lead to differences associated with the progression of the disease. Furthermore, the small sample sizes and the cross-sectional nature of the analysis make any causality assumptions regarding the findings difficult to establish. Further research must thus concentrate on longitudinal data, larger cohorts, and the inclusion of amyloid PET imaging to understand the temporal dynamics of tau propagation.

To sum up, this study offers new perspectives in the search for early biomarkers of AD and for multimodal approaches to the disease, with the goal of improving early detection and characterisation of AD.

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Appendix A

Participants and data

A.1 TR assignment per subject and session

Table A.1: *Repetition times (TR) for each subject and session.*

Subject ID	Session	TR (ms)	Subject ID	Session	TR (ms)
sub-001	ses-20	1500	sub-098	ses-00	1500
sub-002	ses-00	1500	sub-100	ses-01	1700
sub-002	ses-20	1700	sub-102	ses-01	1700
sub-009	ses-00	1500	sub-103	ses-00	1500
sub-013	ses-00	1500	sub-103	ses-01	1700
sub-014	ses-00	1500	sub-104	ses-00	1500
sub-014	ses-10	1500	sub-104	ses-02	1500
sub-016	ses-20	1500	sub-105	ses-01	1700
sub-017	ses-00	1500	sub-106	ses-00	1500
sub-018	ses-00	1500	sub-106	ses-02	1700
sub-019	ses-10	1500	sub-107	ses-01	1700
sub-020	ses-00	1500	sub-108	ses-00	1500
sub-021	ses-00	1500	sub-109	ses-01	1700
sub-022	ses-00	1500	sub-110	ses-00	1500
sub-023	ses-00	1500	sub-110	ses-20	1500
sub-024	ses-00	1500	sub-114	ses-10	1700
sub-024	ses-20	1700	sub-117	ses-00	1500
sub-025	ses-00	1500	sub-118	ses-10	1700
sub-025	ses-10	1500	sub-119	ses-10	1700
sub-025	ses-20	1500	sub-121	ses-00	1500
sub-026	ses-00	1500	sub-122	ses-10	1700
sub-028	ses-00	1500	sub-124	ses-10	1700
sub-030	ses-10	1500	sub-125	ses-10	1700
sub-032	ses-00	1500	sub-126	ses-00	1700
sub-033	ses-00	1500	sub-130	ses-10	1700
sub-034	ses-00	1500	sub-131	ses-00	1700
sub-035	ses-00	1500	sub-131	ses-10	1700
sub-036	ses-00	1500	sub-132	ses-00	1500
sub-037	ses-00	1500	sub-134	ses-00	1500
sub-038	ses-00	1500	sub-136	ses-00	1700
sub-038	ses-20	1700	sub-137	ses-10	1700
sub-039	ses-00	1500	sub-138	ses-10	1700
sub-040	ses-00	1500	sub-139	ses-10	1700
sub-041	ses-00	1500	sub-140	ses-10	1700

Continued on next page

Table A.1: *Repetition times (TR) for each subject and session (continued).*

Subject ID	Session	TR (ms)	Subject ID	Session	TR (ms)
sub-042	ses-00	1500	sub-142	ses-10	1500
sub-043	ses-00	1500	sub-143	ses-10	1700
sub-044	ses-00	1500	sub-144	ses-10	1700
sub-044	ses-10	1500	sub-145	ses-00	1500
sub-045	ses-00	1500	sub-146	ses-10	1700
sub-046	ses-00	1500	sub-148	ses-00	1500
sub-046	ses-10	1500	sub-148	ses-10	1700
sub-047	ses-00	1500	sub-151	ses-00	1500
sub-048	ses-00	1500	sub-151	ses-10	1500
sub-048	ses-10	1500	sub-152	ses-00	1500
sub-048	ses-20	1500	sub-153	ses-00	1500
sub-049	ses-00	1500	sub-154	ses-10	1700
sub-050	ses-00	1500	sub-156	ses-00	1500
sub-051	ses-00	1500	sub-159	ses-00	1500
sub-052	ses-00	1500	sub-160	ses-10	1700
sub-053	ses-00	1500	sub-161	ses-00	1500
sub-054	ses-00	1500	sub-162	ses-00	1500
sub-055	ses-00	1500	sub-162	ses-05	1500
sub-056	ses-00	1500	sub-163	ses-00	1500
sub-057	ses-00	1500	sub-165	ses-00	1500
sub-059	ses-00	1500	sub-166	ses-00	1500
sub-060	ses-00	1500	sub-166	ses-10	1700
sub-061	ses-00	1500	sub-169	ses-00	1500
sub-061	ses-10	1500	sub-171	ses-00	1500
sub-062	ses-00	1500	sub-172	ses-00	1500
sub-063	ses-00	1500	sub-173	ses-00	1500
sub-064	ses-00	1500	sub-174	ses-00	1500
sub-065	ses-00	1500	sub-176	ses-00	1500
sub-065	ses-10	1500	sub-177	ses-00	1500
sub-066	ses-00	1500	sub-178	ses-00	1500
sub-066	ses-20	1700	sub-180	ses-00	1500
sub-067	ses-00	1500	sub-183	ses-00	1500
sub-068	ses-00	1500	sub-185	ses-00	1500
sub-069	ses-00	1500	sub-187	ses-00	1700
sub-069	ses-10	1500	sub-189	ses-00	1500
sub-070	ses-00	1500	sub-190	ses-00	1500
sub-070	ses-10	1500	sub-191	ses-00	1500
sub-071	ses-00	1500	sub-192	ses-00	1500
sub-072	ses-10	1500	sub-195	ses-10	1500
sub-076	ses-00	1500	sub-197	ses-00	1700
sub-077	ses-00	1500	sub-198	ses-00	1700
sub-078	ses-00	1500	sub-204	ses-00	1500
sub-078	ses-10	1500	sub-205	ses-00	1700
sub-079	ses-10	1700	sub-206	ses-00	1500
sub-080	ses-10	1500	sub-207	ses-00	1500
sub-081	ses-10	1700	sub-208	ses-00	1700
sub-082	ses-10	1500	sub-209	ses-00	1700
sub-083	ses-10	1500	sub-211	ses-00	1700
sub-084	ses-00	1500	sub-212	ses-00	1700
sub-084	ses-10	1500	sub-213	ses-00	1700
sub-085	ses-00	1500	sub-214	ses-00	1700
sub-087	ses-10	1500	sub-222	ses-00	1700
sub-088	ses-20	1700	sub-223	ses-00	1700
sub-090	ses-10	1700	sub-224	ses-00	1700
sub-091	ses-00	1500	sub-230	ses-00	1700
sub-091	ses-10	1700	sub-233	ses-00	1700
sub-092	ses-05	1500	sub-235	ses-00	1700

Continued on next page

Table A.1: *Repetition times (TR) for each subject and session (continued).*

Subject ID	Session	TR (ms)	Subject ID	Session	TR (ms)
sub-092	ses-10	1700	sub-238	ses-00	1700
sub-093	ses-00	1500	sub-239	ses-00	1700
sub-093	ses-10	1500	sub-240	ses-00	1700
sub-094	ses-10	1700	sub-241	ses-00	1700
sub-095	ses-00	1500			

Appendix B

Neuropathology reference

B.1 ABC neuropathological score

To quantify the progression of the disease, a neuropathological classification system known as the ABC (ADNC) score is used (Figure B.1).

AD Neuropathologic Change		B¹		
A²	C³	0 or 1	2	3
0	0	Not ⁴	Not ⁴	Not ⁴
1	0 or 1	Low	Low	Low ⁵
	2 or 3 ⁷	Low		
2	Any C	Low ⁶		
3	0 or 1	Low ⁶		
	2 or 3	Low ⁶		

Figure B.1: “ABC” Score for Level of AD Neuropathologic Change. From [4]

This score assesses the three main pathological features of the disease:

- A for A β ;
- B for tau according to Braak stages;
- C for neuritic plaques, corresponding to amyloid plaques associated with neuritic degeneration.

This score allows neuropathological lesions to be linked to clinical symptoms. The higher the score, the greater the likelihood that the lesions explain the symptoms. However,

this correlation between pathology and symptoms is not perfect, as some individuals have a high pathological score without obvious clinical symptoms [5].

B.2 Partial volume effects in PET

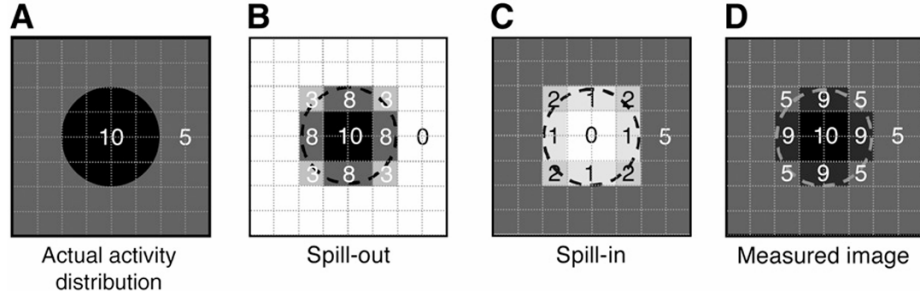


Figure B.2: *Partial Volume Effects in PET.* The true activity distribution (A) is influenced by both the spill-out of activity from the lesion to its surroundings (B) and spill-in from the surroundings to the lesion area (C). As such, the acquired image (D) results from these processes of signal contamination. From [31].

Appendix C

Preprocessing

C.1 fMRIPrep preprocessing workflow

Results included in this manuscript come from preprocessing performed using fMRIPrep 25.2.3 (Esteban et al. (2019); Esteban et al. (2018); RRID:SCR_016216), which is based on Nipype 1.10.0 (K. Gorgolewski et al. (2011); K. J. Gorgolewski et al. (2018); RRID:SCR_002502).

Anatomical data preprocessing The T1w image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.6.2 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OA-SIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL (version unknown), RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using `recon-all` (FreeSurfer 7.3.2, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.6.2), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization and accessed with TemplateFlow (25.0.4, Ciric et al. 2022): ICBM 152 Nonlinear Asymmetrical template version 2009c [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym].

Functional data preprocessing For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume was generated, using a custom methodology of fMRIPrep, for use in head motion correction. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` (FSL, Jenkinson et al. 2002). The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. The aligned T2w image was used for initial co-registration. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, a mask of pixels that likely contain a volume fraction of GM is subtracted from the aCompCor masks. This mask is obtained by dilating a GM mask extracted from the FreeSurfer’s `aseg` segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components’ time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD

or 1.5 standardised DVARS were annotated as motion outliers. Additional nuisance time series were calculated by means of principal components analysis of the signal found within a thin band (crown) of voxels around the edge of the brain, as proposed by (Patriat, Reynolds, and Birn 2017). All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `nittransforms`, configured with cubic B-spline interpolation.

Many internal operations of fMRIPrep use Nilearn 0.11.1 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep’s documentation.

C.2 Time-series extraction workflow

Algorithm 1 Time-series extraction & confound regression C.2

Input Preprocessed BOLD (4D Nifti) · DK parcellation (3D Nifti) · fMRIPrep confounds (.tsv)

Output Cleaned time-series matrix $\mathbf{X} \in \mathbb{R}^{T \times 68}$

PARCELLATION

1. Register DK parcellation onto BOLD grid (*affine transform, nearest-neighbour interpolation*)
2. Keep cortical labels $\in [1001-2999]$, exclude 1000, 2000 (undefined)
3. Map label IDs $\rightarrow$ region names via `FreeSurferColorLUT.txt`
4. Relabel atlas contiguously 1...68 (*required for NiftiLabels-Masker*)

EXTRACTION

5. For each ROI r :
$$x_r(t) = \frac{1}{|M_r|} \sum_{v \in M_r} \text{BOLD}(v, t)$$

CONFOUND REGRESSION

6. Build confound matrix $\mathbf{C} = [\text{trans_x/y/z}, \text{rot_x/y/z}, \text{csf},$
 $]$

7. Regress $\mathbf{C}$ from $\mathbf{X}$: $\mathbf{X}_{\text{clean}} = \mathbf{X} - \mathbf{C}(\mathbf{C}^\top \mathbf{C})^{-1} \mathbf{C}^\top \mathbf{X}$

8. Apply bandpass filter: $\text{high_pass} = 0.005 \text{ Hz}$ (*no low-pass*
applied)

GSR not applied.

Appendix D

Tau accumulation results

D.1 Regional tau statistics

Table D.1: *Post-hoc pairwise comparisons of regional tau SUVR across clinical groups with Bonferroni correction.*

Region	Comparison	U	Raw p-value	Bonferroni p-value	Significance
Entorhinal	CN vs MCI	466.000	< 0.001	< 0.001	***
Entorhinal	CN vs DEM	58.000	< 0.001	< 0.001	***
Entorhinal	MCI vs DEM	503.000	7.6880×10^{-2}	2.3064×10^{-1}	ns
Parahippocampal	CN vs MCI	422.000	< 0.001	< 0.001	***
Parahippocampal	CN vs DEM	39.000	< 0.001	< 0.001	***
Parahippocampal	MCI vs DEM	386.000	2.7220×10^{-3}	8.1670×10^{-3}	**
Inferior temporal	CN vs MCI	403.000	< 0.001	< 0.001	***
Inferior temporal	CN vs DEM	14.000	< 0.001	< 0.001	***
Inferior temporal	MCI vs DEM	324.000	2.6400×10^{-4}	7.9200×10^{-4}	***
Fusiform	CN vs MCI	469.000	< 0.001	< 0.001	***
Fusiform	CN vs DEM	20.000	< 0.001	< 0.001	***
Fusiform	MCI vs DEM	308.000	1.3500×10^{-4}	4.0600×10^{-4}	***

D.2 Tau burden comparison between clinical groups

Region	CN	MCI	DEM	Kruskal H	Kruskal p FDR
bankssts	0,862765	1,797347	3,012678	87,4843838	4,27953E-19
inferiortemporal	0,972729	2,008308	3,005819	100,875656	4,23261E-21
inferiorparietal	0,919581	1,760165	2,964573	93,8687072	2,81305E-20
middletemporal	0,973234	1,841447	2,947566	98,1810154	8,14165E-21
fusiform	0,965673	1,875564	2,852479	97,1566345	9,05863E-21
lateraloccipital	1,023799	1,648795	2,786512	73,4442408	2,25328E-16
entorhinal	1,0319	2,253604	2,675073	90,6612361	9,9895E-20
precuneus	0,846987	1,411998	2,672497	85,3525493	9,9405E-19
isthmuscingulate	0,828873	1,338232	2,619684	92,5809976	4,46292E-20
caudalmiddlefrontal	0,779323	1,422139	2,612459	78,4434329	2,25804E-17
superiorparietal	0,821743	1,464331	2,569151	78,4335063	2,25804E-17
parahippocampal	0,940297	1,82587	2,36504	96,5118068	9,37878E-21
supramarginal	0,842605	1,459764	2,362618	79,0481482	1,93736E-17
posteriorcingulate	0,845027	1,333127	2,352854	76,8347408	4,68744E-17
cuneus	0,936429	1,284108	2,187198	64,1228063	2,02469E-14
rostralmiddlefrontal	0,810143	1,12811	2,120866	52,6586162	5,20708E-12
lingual	0,961915	1,340883	2,120671	72,7723681	2,97774E-16
superiortemporal	0,863499	1,362064	2,093202	86,948003	4,97413E-19
temporalpole	0,91786	1,503048	1,993973	81,9391692	4,97991E-18
parsopercularis	0,779521	1,182618	1,944916	64,6310251	1,65301E-14
parsorbitalis	0,89714	1,062914	1,831686	39,4228451	3,01686E-09
lateralorbitofrontal	0,843308	1,147462	1,796621	61,2541303	8,09271E-14
superiorfrontal	0,757279	1,13667	1,771771	52,9386894	4,72347E-12
parstriangularis	0,844949	1,050237	1,745166	41,2518403	1,29228E-09
frontalpole	0,868216	0,998309	1,604529	19,5552868	5,67053E-05
insula	0,791446	1,173392	1,541154	74,1657489	1,66906E-16
precentral	0,749938	1,062358	1,509215	51,2652317	1,00331E-11
transversetemporal	0,815658	0,971293	1,437947	35,638158	1,88034E-08
postcentral	0,781128	1,044339	1,425505	45,4148529	1,79802E-10
medialorbitofrontal	0,73255	1,008099	1,410431	59,2887728	2,06378E-13
pericalcarine	0,884307	1,01723	1,330513	42,865975	6,1928E-10
paracentral	0,7931	0,988138	1,322573	35,6955393	1,88034E-08
caudalanteriorcingulate	0,78803	1,037473	1,288224	42,0495463	8,9821E-10
rostralanteriorcingulate	0,730706	0,950405	1,189656	40,4949597	1,82385E-09

Figure D.1: *Tau burden comparison between clinical groups, part 1.*

CN vs MCI p Bonferroni	CN vs DEM p Bonferroni	MCI vs DEM p Bonferroni
5,13215E-13	8,25539E-13	0,000931384
1,76858E-16	5,35785E-13	0,000791614
3,59781E-14	4,08245E-13	0,000155389
2,56876E-15	3,86581E-13	0,000135767
1,76367E-15	7,41199E-13	0,000406253
5,75157E-10	2,10514E-11	7,48161E-05
1,5912E-15	5,54492E-12	0,230639716
9,02891E-12	5,35785E-13	6,50389E-05
5,67976E-14	1,07982E-12	3,86036E-05
6,92417E-11	3,46594E-12	0,000288121
7,75936E-11	4,50214E-12	0,000129766
3,45533E-16	2,04621E-12	0,008166966
1,22031E-10	1,07982E-12	0,000357421
3,32647E-10	2,6648E-12	0,000142031
2,42461E-08	6,99374E-11	0,000894423
3,43199E-06	1,23629E-09	0,000568994
1,87297E-09	5,84061E-12	0,000194186
4,97391E-13	1,26781E-12	0,000894423
3,74929E-13	2,00114E-11	0,00968948
4,70177E-08	3,48421E-11	0,000406253
0,000455338	9,06773E-08	0,000406253
4,93575E-08	5,07901E-10	0,000202973
9,59443E-07	2,05174E-09	0,002210991
0,000432929	2,16001E-08	0,00054573
0,444211395	3,89385E-05	0,003599174
2,9218E-11	6,02884E-11	0,00299027
1,30592E-05	3,31109E-10	0,002210991
0,006692521	4,85045E-08	0,000824585
9,73839E-05	1,48742E-09	0,004645259
2,61135E-08	1,18029E-09	0,002573406
7,25755E-06	9,84807E-08	0,018126076
0,000440281	1,36734E-07	0,023338014
5,38315E-05	3,31407E-08	0,005757616
5,69492E-05	4,45838E-08	0,021922386

Figure D.2: Tau burden comparison between clinical groups, part 2.

D.3 Tau SUVr by clinical group and stage

Table D.2: *Median tau SUVr values across stage-like tau regions and clinical groups.*

Clinical group	Early	Intermediate	Late
CN	0.899	0.928	0.831
MCI	1.856	1.645	1.113
DEM	2.287	3.104	2.365

Appendix E

Functional connectivity results

E.1 Node degree group comparisons

Table E.1: *Statistical comparison of mean tau SUVr across node degree tertiles.*

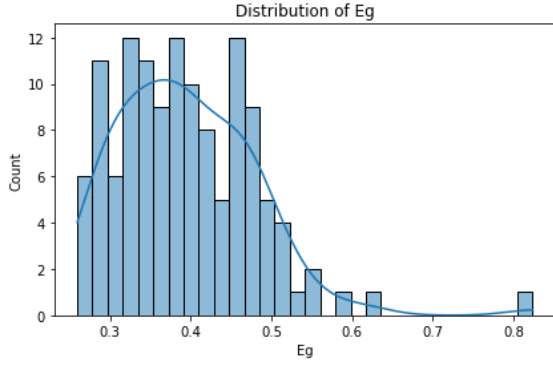
Comparison	Statistic	Raw p-value	Bonferroni p-value
Kruskal–Wallis	$H = 8.48$	–	1.444×10^{-2}
Low vs Medium degree	$U = 204$	2.708×10^{-1}	8.124×10^{-1}
Low vs High degree	$U = 149$	1.152×10^{-2}	3.457×10^{-2}
Medium vs High degree	$U = 153$	2.387×10^{-2}	7.161×10^{-2}

E.2 Post-hoc comparisons of graph metrics

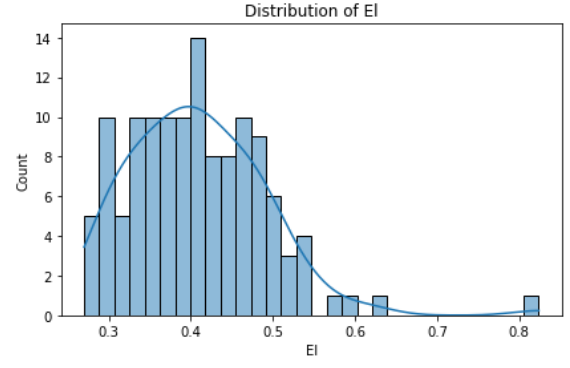
Table E.2: *Post-hoc pairwise comparisons of global and local efficiency across clinical groups with Bonferroni correction.*

Metric	Comparison	U	Raw p-value	Bonferroni p-value
Eg	CN vs MCI	525	9.231×10^{-1}	> 0.999
Eg	CN vs DEM	293	2.903×10^{-2}	8.710×10^{-2}
Eg	MCI vs DEM	630	9.551×10^{-3}	2.865×10^{-2}
El	CN vs MCI	527	9.026×10^{-1}	> 0.999
El	CN vs DEM	296	2.373×10^{-2}	7.119×10^{-2}
El	MCI vs DEM	635	7.757×10^{-3}	2.327×10^{-2}

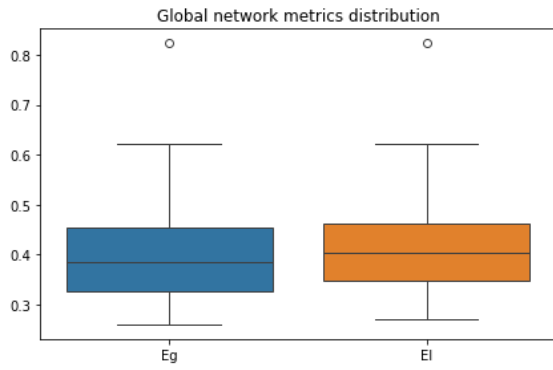
E.3 Distribution of graph metrics



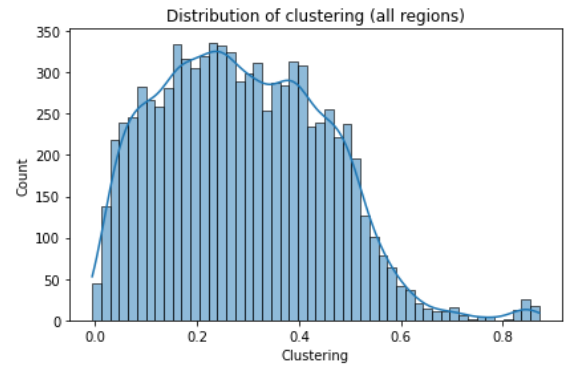
(a) Distribution of E_g .



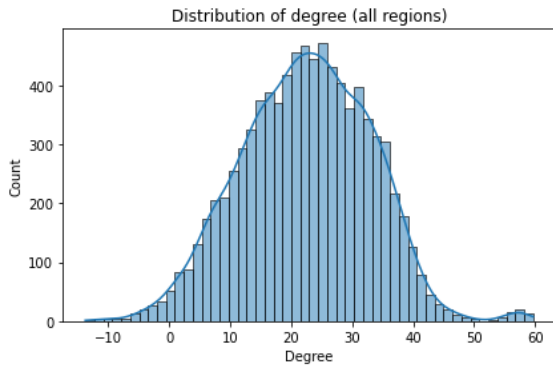
(b) Distribution of E_l .



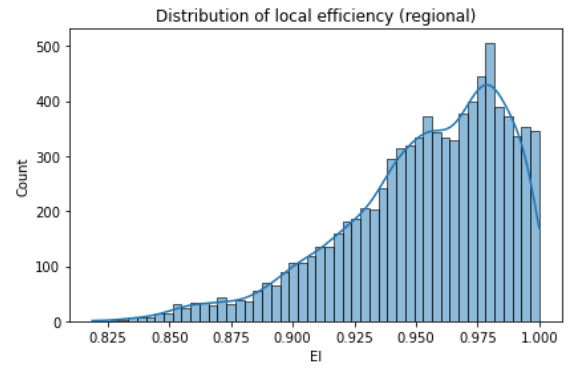
(c) Boxplot of global network metrics.



(d) Distribution of regional clustering coefficient.



(e) Distribution of regional node degree.



(f) Distribution of regional E_l .

Figure E.1: Distribution of graph theory metrics computed from the FC matrices.

E.4 Non-linearity: clustering and degree

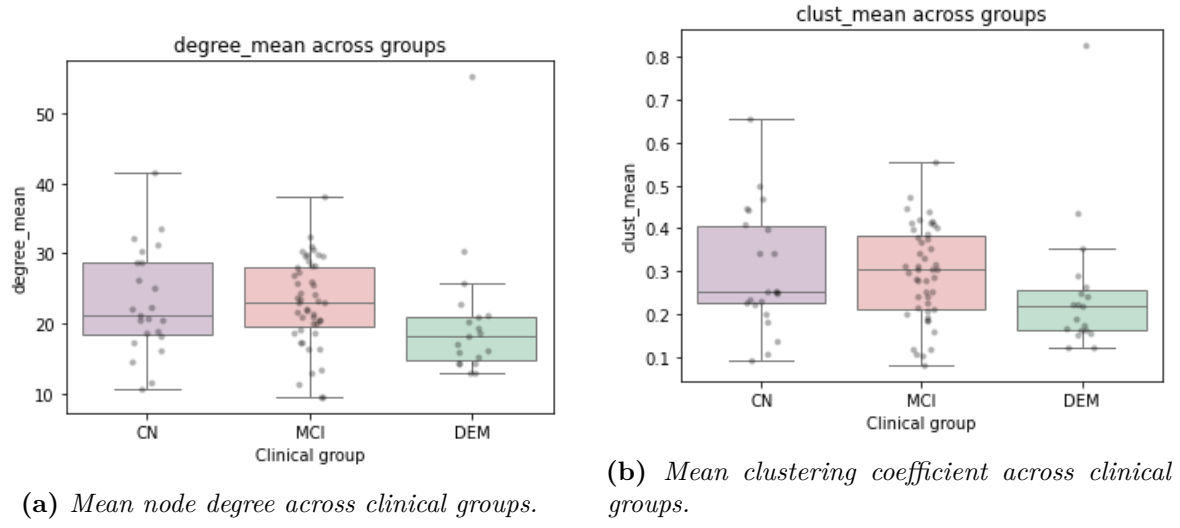


Figure E.2: Boxplots showing the distribution of mean regional metrics across clinical groups. Each point represents an individual observation level value.

E.5 Regional clustering coefficients (68 ROIs)



Figure E.3: Heatmap showing the median values of clustering coefficients for CN, MCI, and DEM groups. Left and right homologous cortical regions were averaged.

E.6 Regional clustering across clinical groups

region_clean	median_CN	median_MCI	median_DEM	H	p_raw	p_fdr
bankssts	0,276942737	0,249570194	0,174840721	4,031571	0,136023	0,265395
caudalmiddlefrontal	0,276123695	0,345867744	0,230888673	4,353714	0,1195	0,265395
cuneus	0,336293572	0,366228496	0,224421136	6,224343	0,049108	0,265395
inferiorparietal	0,358254705	0,389158493	0,281175341	3,83748	0,147683	0,265395
lateralorbitofrontal	0,254975171	0,326578139	0,233806362	4,550616	0,103477	0,265395
lateraloccipital	0,371328148	0,388041589	0,270738486	7,117762	0,028957	0,265395
insula	0,293392918	0,31756459	0,196611151	3,951351	0,140556	0,265395
inferiortemporal	0,337511967	0,369715748	0,256661051	4,831946	0,089372	0,265395
medialorbitofrontal	0,252778644	0,284326483	0,186443733	6,433054	0,082487	0,265395
lingual	0,346592583	0,355488875	0,260384539	5,538437	0,066414	0,265395
postcentral	0,354076096	0,36559015	0,25515011	4,556494	0,107632	0,265395
superiortemporal	0,315889681	0,367561564	0,260780616	4,958203	0,084354	0,265395
precuneus	0,356608137	0,378419726	0,281973692	3,847466	0,146298	0,265395
superiorfrontal	0,297207393	0,355309193	0,244435347	5,10795	0,097841	0,265395
parahippocampal	0,205000146	0,253762343	0,150763844	4,263341	0,121918	0,265395
fusiform	0,31986821	0,370440725	0,249366311	4,808617	0,11211	0,27064
paracentral	0,305194345	0,32385361	0,233089507	3,501153	0,173964	0,271725
pericalcarine	0,314023198	0,331508875	0,231317206	3,774833	0,155205	0,272456
superiorparietal	0,356980414	0,381258382	0,274328675	3,804444	0,158323	0,279236
temporalpole	0,228486286	0,189380675	0,114396618	4,634322	0,128259	0,279236
caudalanteriorcingulate	0,189621991	0,227012777	0,12373671	3,966002	0,15767	0,287096
isthmuscingulate	0,275927644	0,256012278	0,190714721	4,235964	0,1487	0,287096
rostralanteriorcingulate	0,19639706	0,163054862	0,088700879	4,23514	0,147009	0,287096
rostralmiddlefrontal	0,288425527	0,316767542	0,224770044	3,321491	0,19687	0,29207
middletemporal	0,347594196	0,382117538	0,26058543	4,563352	0,158443	0,29807
precentral	0,359254363	0,392658186	0,289946928	2,909521	0,236262	0,310022
posteriorcingulate	0,279994134	0,310206951	0,196784006	3,056368	0,257376	0,357031
parsopercularis	0,223865396	0,259257512	0,208398897	2,479563	0,332323	0,409901
supramarginal	0,34203908	0,339433127	0,273065715	1,845991	0,435202	0,497636
parstriangularis	0,202240529	0,227498975	0,185993083	1,52196	0,499216	0,544974
entorhinal	0,16478281	0,123234244	0,117703187	2,151995	0,492947	0,576769
transversetemporal	0,140700835	0,169393414	0,136190911	1,388419	0,607867	0,645883
frontalpole	0,122064029	0,130498458	0,084843912	1,270857	0,638369	0,662688
parsorbitalis	0,231790371	0,203764016	0,162877376	0,522519	0,782108	0,821642

Figure E.4: Full regional clustering statistics across clinical groups.

E.7 Hierarchical clustering: full region list

Table E.3: *Regional composition of the four ROI clusters. Lateral orbitofrontal and postcentral cortices were present in both clusters 3 and 4.*

Cluster	Regions
1	entorhinal, temporal pole, rostral anterior cingulate, transverse temporal
2	frontal pole
3	caudal middle frontal, cuneus, fusiform, inferior parietal, inferior temporal, insula, lateral occipital, lingual, middle temporal, paracentral, pericalcarine, precentral, precuneus, superior frontal, superior parietal, superior temporal, supramarginal, lateral orbitofrontal, postcentral, posterior cingulate
4	bankssts, caudal anterior cingulate, isthmus cingulate, lateral orbitofrontal, medial orbitofrontal, parahippocampal, pars opercularis, pars orbitalis, pars triangularis, postcentral, posterior cingulate, rostral anterior cingulate, rostral middle frontal, transverse temporal, superior parietal, supramarginal

Appendix F

Tau-connectivity analyses

F.1 Network-level tau similarity statistics

Table F.1: Association between FC and tau similarity by network.

Network	n regions	n pairs	ρ	Classic p-value	Permutation p-value
DMN	10	45	0.823	4.144×10^{-12}	2.000×10^{-4}
Frontal association	8	28	0.711	2.230×10^{-5}	2.000×10^{-4}
Limbic	6	15	0.457	8.668×10^{-2}	6.759×10^{-2}
Visual	8	28	0.381	4.550×10^{-2}	3.319×10^{-2}

F.2 Tau versus Age

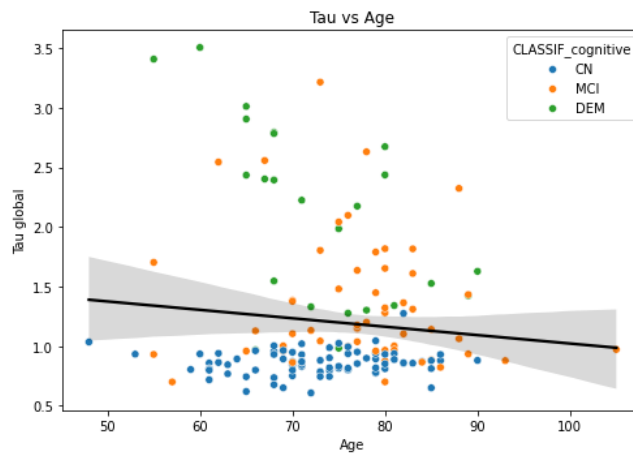


Figure F.1: Age global tau burden correlation for different clinical groups. Each dot in the scatterplot corresponds to one individual patient who is color-coded based on his/her clinical grouping. The black line is the global linear trend with its confidence interval.

As a whole, there was no significant correlation between age and global tau burden (Spearman $r = 0.087$, $p = 0.264$). This correlation was similarly insignificant in the CN ($r = 0.115$, $p = 0.292$) and MCI ($r = -0.134$, $p = 0.326$) groups but significant in the DEM ($r = -0.545$, $p = 0.0059$) group.

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