

**Exploring Functional Connectivity Patterns and
Their Associations with Amyloid and Tau
Biomarkers Across Alzheimer's Disease Stages:
A Resting-State fMRI Study**

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Declaration of Originality

I confirm that this thesis is the result of my own independent work. All sources used in the preparation of this thesis have been duly acknowledged and referenced.

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline and hallmark biomarkers: amyloid-beta ($A\beta$) plaques and neurofibrillary tau tangles. Functional connectivity, assessed via resting-state functional Magnetic Resonance Imaging (fMRI), has shown associations with $A\beta$ and tau. However, its adoption is hindered by high data dimensionality, noise, and artefact susceptibility.

This study explored functional connectivity differences across clinically relevant AD groups, aiming to enhance our understanding of the link between brain function and AD neuropathology.

Methods and Data Analysis: Two datasets were used for cross-sectional analyses: dataset 1 was comprised of cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia of the Alzheimer's Disease type (DAT) participants. Dataset 2 included CU only. Whole-brain region-of-interest (ROI)-to-ROI analysis was followed by a dual-approach of Multivariate Pattern Analysis and seed-based connectivity to identify regions and measure group differences in functional connectivity patterns. We then investigated whether AD biomarkers moderate functional connectivity and cognition relationships.

Lastly, network-level functional connectivity differences within and between the Default Mode network and medial temporal lobe (MTL) were measured between CU $A\beta^+$ and $A\beta^-$ participants.

Results: Multivariate Pattern Analysis revealed functional connectivity differences between two out of three group comparisons. The left thalamus, precuneus, and frontal gyri sub-regions were identified as key ROIs. Tau (more than $A\beta$) moderated more relationships between functional connectivity and cognition, particularly among MCI participants.

In dataset 2, CU $A\beta^+$ participants showed more relationships between MTL functional connectivity and regional tau burden. Specifically, among $A\beta^+$, lower functional connectivity was associated with higher tau pathology, pointing towards early neurodegeneration.

Conclusions: These findings enhance our understanding of the interplay between brain function and AD pathology, reinforce tau as a biomarker closely linked to functional connectivity, and identify

specific brain regions and networks with potential clinical applications in early AD diagnosis and therapeutic interventions.

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List of Abbreviations

AAL	Automated Anatomical Labelling Atlas
A β	Amyloid-Beta
AD	Alzheimer's Disease
ADNI(-3)	Alzheimer's Disease Neuroimaging Initiative (-phase 3)
ANOVA	Analysis of Variance
APA	American Psychological Association
APOE	Apolipoprotein
AT[N]	Amyloid, Tau, and Neurodegeneration Framework
A.u	Arbitrary Units
BOLD	Blood Oxygen Level Dependent (response)
C1 ... C10	Cluster 1 ... Cluster 10
CDR	Clinical Dementia Rating (scale)
CN	Cognitively Normal
CSF	Cerebrospinal Fluid
DAT	Dementia Due to Alzheimer's Disease
DF	Degrees of Freedom
DSM(-I, -II, -III, -IV)	Diagnostic and Statistical Manual (1-4)
fALFF	Fractional Amplitude of Low-Frequency Fluctuations
FDR	False Discovery Rate
(MET-)FINGER	(Metformin and) Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
(f)MRI	(Functional) Magnetic Resonance Imaging
FSL	Functional Magnetic Resonance Imaging of the Brain Software Library
FWE	Family Wise Error

ICV	Intracranial Volume
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MTL	Medial Temporal Lobe
NHS	National Health Service
PC(A)	Principal Component(s Analysis)
PET	Positron Emission Tomography
OASIS(-3)	Open Access Series of Imaging Studies (-phase 3)
ROI(s)	Region(s) Of Interest(s)
SD	Standard Deviation
SE	Standard Error
SPM(12)	Statistical Parametric Mapping (12)
SUVr	Standardised Uptake Value Ratio
TBV	Total Brain Volume
TFCE	Threshold Free Cluster Enhancement
UK	United Kingdom

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List of Symbols

Symbol	Definition
$A\beta$	Amyloid-Beta
B_0	Main Magnetic Field
B_1	Radiofrequency Pulse
Δ	Change or Difference
$\epsilon 2, \epsilon 3, \epsilon 4$	Genetic Variants Related to the <i>APOE</i> Gene
F	Statistical Test Related to ANOVA
M	Mean, Moderator
p	Probability Value
R^2	How Well the Regression Line Approximates the Actual Data
T1	Longitudinal Relaxation Time
T2	Transverse Relaxation Time
T2*	The Rate at Which Transverse Magnetisation Decays in an MRI Sequence Due to Both Spin-Spin Relaxation and Magnetic Field Inhomogeneities
TA	Acquisition Time
TE	Echo Time
TR	Repetition Time
W	Shapiro-Wilk Test of Normality
x, y, z	Coordinates, Variables (Moderation)
β and γ	Beta- and Gamma-Secretase
μ	Magnetic Permeability
V	Vertices / Nodes (Graph Theory), e.g., Brain Regions
E	Edges Between Vertices / Nodes (Graph Theory), e.g., Statistical Dependencies
i	Brain Region i Functionally Connected to Region j
j	Brain Region j Functionally Connected to Region i

ρ	Spearman's Rank Correlation Coefficient
n	Number
d^2	The Square of the Difference in the Ranks of the Two Variables for Each Data Pair in Spearman's Rank

Chapter 1: Introduction

1.1 A Brief Historical Summary of Alzheimer's Disease and Dementia

Our understanding of Alzheimer's disease (AD) has evolved, driven by advancements in clinical techniques, the validation of fluid biomarkers, and improvements in imaging technology (Van Oostveen & De Lange, 2021; Peng et al., 2023; Korologou-Linden et al., 2024). AD, a form of dementia, is a highly complex and multifactorial disease resulting from complex and poorly understood interactions between diverse modifiable and non-modifiable factors (as described in a textbook by Kumar et al., 2024). Although significant advancements have significantly broadened our understanding of the precise biological mechanisms underpinning this disease, they remain unknown (García-Morales et al., 2021).

As Yang et al. (2016) noted, the etymology of the term 'dementia' can be traced back to around 600 A.D. by Saint Isidore of Seville (c. 560 - 636 A.D.). Its Latin origin refers to a state of mind. Thus, historical concepts underlying the research of dementia symptoms significantly predate the 20th century. However, in 1907, Alois Alzheimer paved the way for the modern definition of AD through his pivotal work.

Hippius and Neundörfer (2003) provided a historical account of the discovery of AD. They described that, in 1906, Alois Alzheimer investigated the brain of Auguste D. after her death, identifying plaques and neurofibrillary tangles - key pathological features of AD (Alzheimer, 1907). Initially, his findings received little attention, but Emil Kraepelin recognised their significance and introduced the term "Alzheimer's disease" in his 1910 psychiatric textbook (Ramirez-Bermudez, 2012). In 1911, Alzheimer studied another patient, Josef F., whose brain exhibited plaques but lacked neurofibrillary tangles. This led to uncertainty about whether such cases were part of the same condition. Decades later, modern research reanalysed both cases and confirmed that plaque-only cases and neurofibrillary tangle-only cases are simply different stages in the development of the same disease process. Alzheimer's pioneering work laid the foundation for understanding dementia, and his contributions are now widely recognised (Hippius & Neundörfer, 2003).

The clinical definitions of AD have evolved, partly due to changes in its diagnostic criteria. The Diagnostic and Statistical Manual of Mental Disorders (DSM), currently in its fifth edition, is an essential tool guiding clinicians in the classification of mental disorders, including AD. DSM-I, published in 1952, made no mention of “dementia” bar a brief description under “Schizophrenic Reactions”, in which schizophrenia was defined broadly as a disturbance in perceptions of reality (American Psychological Association [APA], 1952). Years later, in DSM-II (1968), the first clinical definition of “dementia” was described by differentiating between senile and pre-senile subtypes based on the patient’s age of symptom onset (APA, 1968). DSM-III-Revised (1987) expanded on previous classifications by categorising both presenile and senile dementias under the umbrella term “primary degenerative dementia”, which was further divided into two forms: senile-onset primary degenerative dementia of Alzheimer’s disease (occurring in individuals over 65) and presenile types (occurring in individuals under 65). In 1994, the DSM-IV illustrated AD with greater sophistication and was enriched with detailed biological and cultural feature descriptions. DSM-IV cited dementia as ... “characterized by the development of multiple cognitive deficits (including memory impairment) that are due to the direct physiological effects of a general medical condition, to the persisting effects of a substance, or multiple etiologies” (APA, 1994). Lastly, the most recent addition, DSM-V (2013) made significant changes to the disease’s nomenclature (APA, 2013). For example, replacing the term “dementia” with major and minor neurocognitive disorders (APA, 2013). More recent developments expanding from foundational concepts to include hallmark pathological biomarkers will be covered in further detail later in this chapter. In the present day, AD (and other forms of dementia) presents a significant societal and financial burden worldwide.

1.2 Epidemiology and Cost of AD

1.2.1 Epidemiology

In addition to the significant deficits in memory, thinking, and functionality faced by individuals with AD, it presents a more comprehensive, multidimensional, and societal problem in many parts of the world, including the United Kingdom (UK). This issue impacts society (internally and

domestically), the health infrastructure supporting patients (the National Health Service [NHS]), and caregivers.

Worldwide life expectancy has increased on average (Aburto et al., 2020). Consequently, with an ageing global population, the number of people with AD is expected to rise exponentially over the next few decades and beyond (“*2020 Alzheimer's Disease Facts and Figures*”, Alzheimer's Association, 2020). Between 1990 and 2019, the global incidence and prevalence of AD and other dementias increased by 147.95% (incidence) and 160.84% (prevalence; Li et al., 2022). Therefore, AD presents a public health crisis that should not be understated (Macklin, 2021).

A concerning prediction estimates that, by 2040, the number of people with AD in England will increase to nearly 1.6 million (Wittenberg et al., 2020). Already in 2022, AD and dementia were the leading cause of death in England and Wales, accounting for 11.40% of total deaths (“*Death Registration Summary Statistics, England and Wales: 2022*”, Office for National Statistics, 2023). AD is also being diagnosed more frequently. In the UK, “[National Health Service] NHS staff have diagnosed 475,573 people with dementia in September [2023] - up more than 52,000 than the same time last year” (“*NHS Dementia Diagnosis Rates at Three-Year High*”, NHS, 2023).

1.2.1 Cost of AD

The global cost of dementia was \$1.3 trillion in 2019 (“*World Alzheimer Report*”, Alzheimer's Disease International, 2023). AD and dementia rates significantly impact overall social care costs. For example, in 2021, the estimated cost of dementia in the UK was £25 billion. By 2050, this is predicted to almost double to £47 billion (“*The Economic Impact of Dementia*”, Alzheimer's Research UK, n, d). In addition to *direct* healthcare costs, informal care contributes significantly to the overall (or ‘*indirect*’) societal burden of AD and dementia, and the cost of which is often the strain on families. Informal care refers to unpaid, ongoing assistance with daily living activities provided by a person to someone else with a chronic illness or disability (Roth et al., 2015). With the UK's ageing population, the demand for unpaid care is expected to rise significantly. This emphasises the growing challenge families and the wider community face (Wittenberg et al., 2020).

However, Ferrari and Sorbi, within their 2021 review article, state that despite the growing urgency within the scientific community, a cure still needs to be discovered. AD is believed to be an “evolving puzzle”, characterised by its high heterogeneity and a wide range of modifiable and non-modifiable risk factors (Ferrari & Sorbi, 2021). These risk factors interact, contributing to their incredibly complex and multifaceted nature (Ferrari & Sorbi, 2021). As such, it is imperative to untangle these complex interactions and reveal the potential underlying mechanisms underpinning AD (Calabrò et al., 2021).

1.3 AD Nosology

Understanding these complexities becomes even more critical when we consider that AD is just one form of dementia. Dementia is an umbrella term, encapsulating multiple neurodegenerative diseases as an overarching category (Holmes & Amin, 2020). AD is the most common form of dementia, accounting for approximately 60 - 70% of worldwide cases (“*Dementia*”, World Health Organisation, 2023). Other less common forms of dementia include vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (“*Dementia*”, World Health Organisation, 2023).

Individuals with AD experience “progressive loss of episodic memory and cognitive function, with later deficiency of language and visuospatial abilities”, indicative of a gradual decline of memory, thinking, and functionality over time (Silva et al., 2019). In Kumar et al.’s 2022 textbook “*Alzheimer Disease*”, AD typically exhibits an insidious onset, with symptoms worsening gradually (Kumar et al., 2022), and evidence suggests that exposure to AD risk factors and brain changes can begin as early as mid-life (Ritchie et al., 2015).

In 1984, a collaborative group, including the National Institute of Neurological and Communicative Disorders and Stroke, along with the Alzheimer's Disease and Related Disorders Association, established diagnostic criteria for AD. These criteria delineated syndromal, categorical diagnoses for probable, possible, and definite cases of AD (McKhann et al., 1984). Twenty-seven years later, the 2011 National Institute on Ageing and Alzheimer’s Association published their guiding principles for AD diagnosis (Albert et al., 2011; McKhann et al., 2011). These guidelines defined three primary stages of

AD: preclinical, Mild Cognitive Impairment (MCI), and dementia (see Figure 1.1.). They also outlined specific diagnostic criteria for each stage, focusing on symptomatic AD progression (Albert et al., 2011; McKhann et al., 2011). Sperling et al. (2011) introduced this “preclinical AD” concept and offered clinical diagnostic recommendations. Their work aimed to establish diagnostic guidelines and create a unified framework and common terminology to enhance communication within the field.

Later, in 2016, Jack et al. (2016) proposed the binarised “AT[N]” classification scheme, in which individuals are given an amyloid (A), tau (T), and neurodegeneration (N) classification of either positive (+) or negative (-) to create individualised signatures, e.g., one might appear as ranging from A-/T-/N- to A+/T+/N+, and every cross-combination in-between (the means to which these biomarkers are measured is described in Table 1.1.). Although undoubtedly influential, the paper has been widely debated. An example is the lack of consideration for the so-called “peri-threshold individuals” (McRae-McKee et al., 2019). In this case, those who occupy a ‘grey zone’ are defined as the “interval around the threshold within which we lose the ability to differentiate between the subsequent cognitive trajectories of biomarker normal/abnormal individuals” (McRae-McKee et al., 2019). Therefore, this questions whether these biological signatures encapsulate AD heterogeneity and individual differences. There is ample evidence suggesting AD, as a disease, operates along a continuum regarding the relative inter-individual differences in possessed risk factors (Aisen et al., 2017). This may partly explain AD’s complexity. Increased understanding of other risk factors in AD development has led some researchers to seek a broadening of the biomarker matrix approach - “ATX[N].” Whereby “X” represents novel biomarkers such as synaptic dysfunction markers, blood-brain barrier alterations, etc. (as described in a review by Hampel et al., 2021).

Further AT[N] framework issues stem from these three imaging biomarkers’ poor correlation with clinical symptoms. A quote by Tarawneh (2020) sums up this sentiment effectively by stating, “There is a significant degree of heterogeneity among individuals with the same clinical phenotype regarding the number, degree, and distribution of different pathologies in the brain, and their rate of progression over time” (Tarawneh, 2020). For example, imagine two people with similar levels of pathology across all three components (AT[N]). One person may develop significant deficits in cognitive performance and functionality that warrant a clinical diagnosis of AD, and one may not. This presents substantial

problems for developing disease-modifying drugs that target specific molecules within the brain. Asymptomatic older adults with no clinical symptoms - but still demonstrating biomarkers above a pre-defined threshold - would, under the AT[N] criteria, be categorised as falling along the *disease* continuum. A concern echoed by a set of recommendations from the International Working Group stating that AD-related biomarkers fall along a continuous scale and that a binary threshold “does not reflect the reality of amyloid β and tau pathology” (Dubois et al., 2021).

More recently, Jack et al. (2024) defined AD as a biological process that begins with “AD neuropathologic changes” (ADNPC) in asymptomatic individuals, with disease progression leading to clinical symptoms (e.g., cognitive decline). They defined core biomarkers (termed “Core 1”), including A β -PET, cerebrospinal fluid (CSF) biomarkers, and plasma phosphorylated-tau 217, that indicate the presence of ADNPC, encompassing both amyloid plaques and tau tangles. An abnormal “Core 1” biomarker is sufficient for an AD diagnosis and clinical decision-making (Jack et al., 2024). Later biomarkers (termed “Core 2”), such as tau-PET and biofluid markers, provide prognostic insights and enhance diagnostic confidence. This staging model integrates biological and clinical factors, accounting for co-pathologies, cognitive reserve, and brain resistance (Jack et al., 2024). Furthermore, the International Working Group continues to define AD as a clinical-biological entity, diagnosing this disease based on a characteristic clinical phenotype supported by pathophysiological biomarkers (CSF, A β - or tau-PET, or plasma phosphorylated-tau 217, pending clinical approval; Dubois et al., 2024).

Table 1.1. AT[N] Alzheimer's disease biomarkers and their measurements

	Biomarker description	Measurement
<i>Amyloid</i>	Aggregated A β plaques	• CSF A β_{42}
		• A $\beta_{42} / 40$ ratio
		• A β -PET
<i>Tau</i>	Aggregated tau (forming neurofibrillary tangles)	• CSF phosphorylated tau,
		• Tau-PET.
<i>Neurodegeneration</i>	Neurodegeneration or evidence of neuronal injury	• Anatomic (structural) MRI
		• F-18 fluorodeoxyglucose - PET
		• CSF total tau

Notes: A β = amyloid-beta; CSF = cerebrospinal fluid; PET = positron emission tomography.

AD presents a further complexity with its subdivisions into early-onset and late-onset variants. Early-onset AD manifests much earlier than late-onset AD (before age 65; Goate et al., 1991). On the other hand, late-onset AD typically occurs later in life, commonly after age 65. AD is diagnosed in approximately 10% of individuals aged 65 and older, with prevalence increasing significantly with age, reaching up to 40% among those over 80 years (Schultz et al., 2004). This thesis will focus on the late-onset variant of AD.

Research to date has revealed numerous non-modifiable and modifiable risk factors associated with an increased likelihood of developing AD (Rabinovici, 2019). Late-onset AD is thought to arise from both genetic and environmental risk factors (Eid et al., 2019).

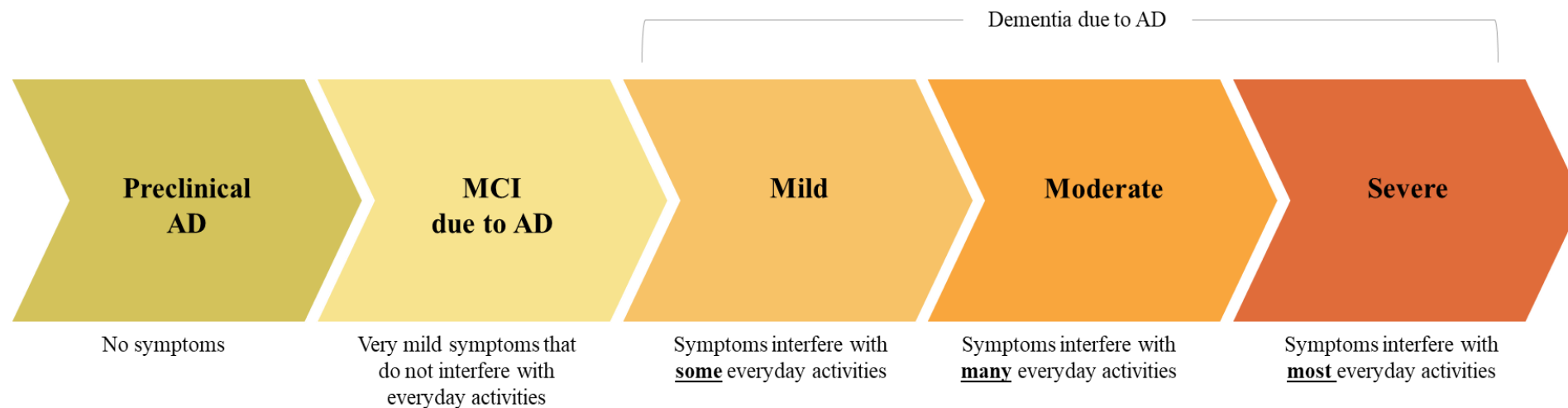


Figure 1.1. Schematic illustrating Alzheimer's Disease staging

Note: Adapted from “2020 Alzheimer's Disease Facts and Figures” (Alzheimer's Association, 2020).

AD = Alzheimer's disease; MCI = mild cognitive impairment. MCI = Mild Cognitive Impairment.

Image showing the progressive nature of AD, beginning at the preclinical stages in which no symptoms are observed, through to MCI due to AD (very mild symptoms that do not interfere with everyday activities), and AD: mild, moderate, and severe.

1.4 Clinical Features and Biomarkers

1.4.1 Clinical Features

The integral symptom of AD is cognitive decline. According to a review by Khera and Rangasamy (2021), cognitive decline is defined as the “brain’s ability to acquire, process, store, and retrieve information” (Khera & Rangasamy, 2021). Cognition across AD stages can be evaluated using a range of well-validated tools. Examples include the clinical dementia rating scale (CDR; Morris, 1993), the Mini-Mental State Examination (MMSE; Folstein et al., 1975), the Montreal Cognitive Assessment (Nasreddine et al., 2005), and the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph et al., 1998), among many others. These tools serve various purposes, from providing clinical insights into cognitive decline with input from a study partner (someone who knows the participant well) to assessing multidomain cognitive performance (e.g., memory, visuospatial processing, executive function, etc.).

Aiding in diagnosing AD are hallmark biomarkers that indicate the presence and accumulation of pathological features. AD is characterised pathologically by the presence of amyloid- β (A β) plaques and neurofibrillary tangles composed of hyperphosphorylated tau (Montine et al., 2011; Jack et al., 2018). These biomarkers can be assessed using various brain imaging modalities, which will be detailed further in subsequent sections.

1.4.2 Imaging Biomarkers

1.4.2.1 Amyloid

The pathological role of A β in AD development gave rise to the “amyloid hypothesis” (also known as the “amyloid cascade hypothesis”), as described in a review by Karran et al. (2011). This theory posits that the accumulation of amyloid plays a central role in the development and progression of AD (Hardy & Higgins, 1992; Hardy & Selkoe, 2002). These plaques are formed through mutations of the amyloid precursor protein and the sequential proteolytic cleavage of amyloid precursor protein by β - and γ -secretase enzymes (Zhang et al., 2010; see also Figure 1.2.).

Linked with increased A β is cerebral amyloid angiopathy, characterised by the deposition of A β on the blood vessels within the brain (Ghisso et al., 2010). A β is associated with haemorrhagic and ischemic lesions, encephalopathy, and, notably for this project, dementia (Liao et al., 2017). Cerebral amyloid angiopathy might contribute to AD's pathogenesis by affecting perivascular drainage, affecting the extent to which A β is cleared from the brain (as described in a review by Greenberg et al., 2020).

1.4.2.2 Tau

Another hallmark neuropathological AD biomarker is tau. Tau is a protein-stabilising neuronal microtubule highly expressed within the central nervous system (Muralidar et al., 2020). Microtubules are essential for numerous cellular processes (e.g., intracellular transportation, cell division, and cell morphogenesis; Goodson et al., 1997). Modifications (e.g., prion-like dispersions) can lead to abnormal tau folding and hyperphosphorylated tau (Khatoon et al., 1994). Ultimately leading to tau oligomerisation and neurofibrillary tau tangles (Lin et al., 2007). The clinical consequences of tau accumulation are that, unlike A β , a higher tau burden was associated with decreased cognition among both early- and late-onset AD (Tanner et al., 2021).

Tau spread tends to begin within the entorhinal cortex, spread to limbic regions, and eventually to associative cortices (Braak & Braak, 1991; 1995; Figure 1.3.). Unlike A β , tau is associated with cortical atrophy (Malpetti et al., 2022). However, the observed co-occurrence of cortical A β alongside extra-limbic tau may suggest that the former facilitates the latter's spread outside the medial temporal lobe (MTL; Vogel et al., 2020). Moreover, Vogel et al. (2021) found four distinct types of tau spread. The researchers reaffirmed the existence of limbic-predominant and MTL-sparing tau spread patterns and found evidence for "atypical sub-types": posterior and lateral temporal patterns (Vogel et al., 2021). Suggesting that individual differences in tau spread may be present among some older adults, depending on their demographic and cognitive profiles (Vogel et al., 2021).

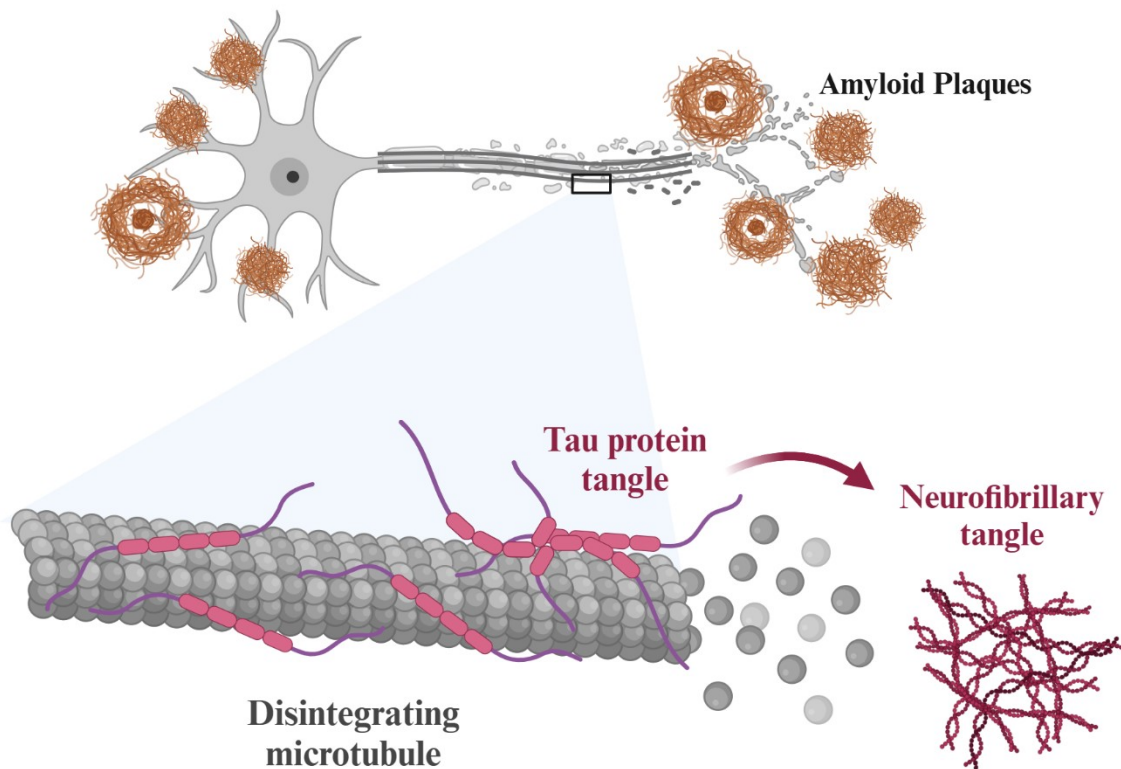


Figure 1.2. Image depicting the relationships between A β plaques and neurofibrillary tau tangles

Note:

1. A β plaques are extracellular deposits of A β that accumulate around neurons. They disrupt cell communication and trigger inflammatory responses (Zhang et al., 2010).
2. Neurofibrillary tau tangles occur within neurons due to the aggregation of hyperphosphorylated tau (Malpetti et al., 2022). Tau typically stabilises microtubules, but when it becomes dysfunctional, it detaches, causing the microtubules to disintegrate. Tau then aggregates, forming tangles (Malpetti et al., 2022).

Created with Biorender.com.

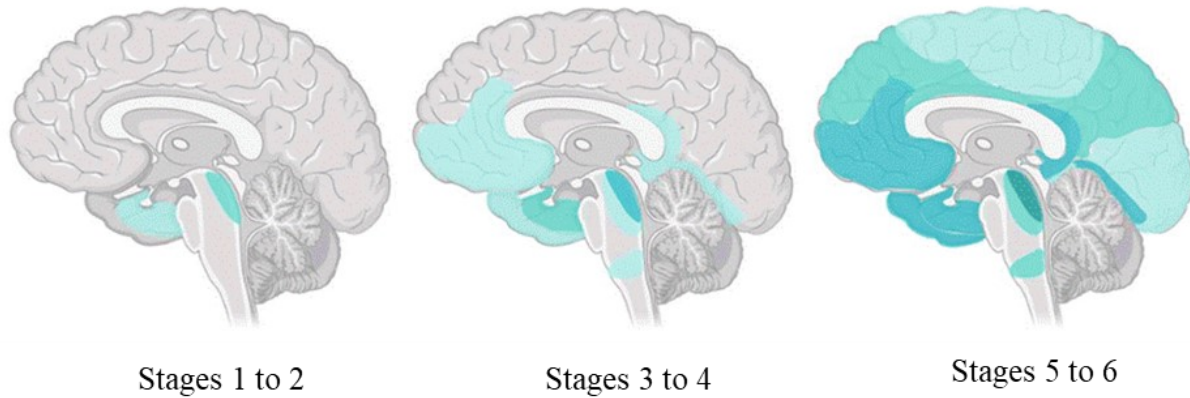


Figure 1.3. Image adapted from Braak & Braak (1991) showing the spread of neurofibrillary tau tangles between Braak stages 1 to 6.

Note: Blue/green = spread of tau between brain regions.

The image depicts the spread of tau. Stages 1 and 2 are the transentorhinal stage, stages 3 and 4 are the limbic stage (hippocampus, amygdala, and other limbic structures), and stages 5 and 6 are the neocortical stage (across the neocortex).

The colour scale illustrates brain regions commonly associated with tau pathology at each Braak stage. The shades correspond to Braak staging images, using varying intensities to depict both the severity of tau accumulation and the affected areas. Darker shades generally indicate greater tau deposition, while lighter colours generally indicate regions with lower tau pathology.

Created with Biorender.com.

1.4.2.3 Neurodegeneration

Neurodegenerative disorders (such as AD) are characterised by neuronal loss (Przedborski et al., 2003). Briefly, neurodegeneration (or neuronal injury) is difficult to define in relation to AD, as the exact causes of neurodegeneration can result from many causes and contributors (and are therefore unknown; Jack et al., 2016). There is also uncertainty as to the extent to which neurodegeneration is

caused by AD versus other conditions (Jack et al., 2016). Note that measures of neurodegeneration fall out of scope for this thesis.

1.4.3 CSF and Blood-Based Biomarkers

Significant investment in expenditure is needed for the technical infrastructure required for positron emission tomography (PET)-based imaging of AD pathological biomarkers – amyloid and tau (Self & Holtzman, 2023). Recent advances in fluid-based assays detect the presence of proteins in CSF and blood plasma, making them potentially a sensitive and accessible alternative to neuroimaging modalities (Self & Holtzman, 2023). These biomarker assays can detect a variety of AD pathological biomarkers ($A\beta$ and tau) as well as neuroinflammatory proteins (e.g., glial fibrillary acidic protein) and markers of neuronal dysfunction and degeneration (e.g., synaptic proteins), among others (Self & Holtzman, 2023).

Existing CSF biomarkers such as phosphorylated-tau, total-tau, and $A\beta$ (specifically $A\beta_{42}$ [denoting the 42-amino acid form of $A\beta$]) aid in the diagnosis of AD (Dubois et al., 2007). For example, one study found that CSF $A\beta_{42}$ could differentiate patients with AD dementia from those with frontotemporal dementia with a sensitivity and specificity of 85% and 77%, respectively (Ewers et al., 2015). Additionally, research by Spies et al. (2010) found the CSF $A\beta_{40} / A\beta_{42}$ ratio to increase the differential diagnosis of AD with other dementias.

Lumbar punctures are cheaper than PET (Contador et al., 2022), but cannot visually understand pathology aggregation and spread. For example, Wolters et al. (2020) found that elevated tau CSF levels appeared to precede tau imaging manifestation (via tau-PET). Still, the latter provides valuable topographic information (Wolters et al., 2020).

The recent emergence of blood-based biomarkers provides a less invasive diagnostic tool compared to measures of collecting CSF. It may even replace CSF and PET markers in determining participant eligibility for AD clinical trials and cohort studies (Korologou-Linden et al., 2024). Blood-based biomarkers can also be scaled to meet primary care settings' needs, thus demonstrating their potential

as a cost-effective yet patient-centred tool for AD diagnostic and treatment purposes (Korologou-Linden et al., 2024).

In summary, numerous ways exist to visualise and measure hallmark AD pathological biomarkers. Yet our understanding of the underlying mechanisms of AD is clouded by many modifiable and non-modifiable risk factors that interact in complex ways, leading to numerous clinical pathways toward diagnosing AD (Calabrò et al., 2021). The following section will highlight some of these risk factors.

1.5 AD Risk Factors

Risk factors are either modifiable or non-modifiable (Loeffler, 2021). One's age, genetics, biological sex, and ethnicity are all examples of *non-modifiable* risk factors, whereas environmental risk factors are *modifiable* (to which there are many; Loeffler, 2021). The aetiopathogenesis of AD is complex, with many factors that can contribute to its development, making AD a highly heterogeneous condition (Ferreira et al., 2018).

1.5.1 Non-Modifiable Risk Factors

Firstly, age is the most significant risk factor of late-onset AD (Silva et al., 2019) and mainly affects older adults over the age of 65 years ("*Alzheimer's Disease*," 2024, NHS). The likelihood of developing AD increases substantially as individuals age, and according to the Alzheimer's Association, the risk of AD doubles approximately every five years after the age of 65; by the age of 85, the risk reaches nearly one-third ("*2024 Alzheimer's Disease facts and Figures*", Alzheimer's Association, 2024).

Next, the human Apolipoprotein E (*APOE*) gene was identified as a significant genetic risk factor for AD (Corder et al., 1993; Strittmatter et al., 1993). Subsequently, the $\epsilon 4$ allele of the *APOE* gene was identified as the most potent genetic risk factor for cerebral amyloid angiopathy and AD (Farrer et al., 1997). The *APOE* gene has three different alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, with the $\epsilon 4$ allele being the most potent known genetic risk factor for AD (Roses, 1996). All humans inherit two alleles, resulting in six possible combinations: $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$. Individuals with different variants of alleles

are categorised as heterozygous ($\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, and $\epsilon 3/\epsilon 4$), while those with the same variants are homozygous ($\epsilon 2/\epsilon 2$, $\epsilon 3/\epsilon 3$, and $\epsilon 4/\epsilon 4$). There has been considerable debate and research regarding the relative risk of developing AD among older adults with heterozygous and homozygous risk genes ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$ [heterozygous] vs $\epsilon 4/\epsilon 4$ [homozygous]). For instance, $\epsilon 2$ was previously considered neuroprotective against AD (Corder et al., 1993). However, a recent review by Kim et al. (2022) found that while $\epsilon 2$ showed significant associations with longevity and AD neuropathologies, its correlation with AD imaging biomarkers and cognitive performance was inconsistent.

The third non-modifiable risk factor, sex, pertains to differences in gonadal hormones, hormone cycles, and sex chromosomes (X and Y), as these are all important contextual factors when considering sex-related differences in AD (Castro-Aldrete et al., 2023). Considerations of the broader socio-economic and socio-cultural constructs disproportionately affecting women are also important (Castro-Aldrete et al., 2023).

Lastly, for ethnicity, one systematic review and meta-analysis found the pooled risk ratio for dementia incidence when comparing Black and White ethnic groups was 1.33 (95% confidence interval [CI]= 1.07 - 1.65; Shiekh et al., 2021). Whereas the pooled risk ratio for dementia incidence between Asian and White ethnic groups was lower (.86, 95%), suggesting ethnic differences in dementia risk (Shiekh et al., 2021). Both sex and ethnic differences in outcomes of dementia trials point towards further complexities in the forms of biological and sociocultural differences in the broader population.

1.5.2 Modifiable Risk Factors

The 2020 Lancet Commission Report highlighted 12 modifiable risk factors for dementia that could serve as prevention targets: lower levels of education, hypertension, hearing impairment, depression, physical inactivity, diabetes, smoking, alcohol consumption, infrequent social contact, brain trauma, air pollution, and obesity (Livingston et al., 2020). According to their report, modifying and treating these risk factors could potentially prevent or delay up to 40% of dementia cases, emphasising the critical importance of public health programs and targeted interventions for dementia prevention (Livingston et al., 2020). More recently, in their 2024 report, two new modifiable risk factors were added in 2024:

vision loss and high low-density lipoprotein cholesterol (Livingston et al., 2024). The current number of modifiable risk factors is 14 (Livingston et al., 2024).

Lifestyle risk factors can be measured via lifestyle interventions. One example is the “Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability” (FINGER) study (Kivipelto et al., 2013). This two-year multidomain intervention combined nutritional guidance, cognitive training, social activity, and guidance in managing vascular and metabolic risk factors. The findings show that multidomain interventions could improve or maintain cognitive function in at-risk older adults (Ngandu et al., 2015). The FINGER trial has since been applied to many other countries across the globe (Kivipelto et al., 2020), including the UK, which is currently in progress (termed “MET-FINGER”; Barbera et al., 2024). There has been a move toward precision medicine approaches to treating the individual. It is defined as using biomarkers (e.g., genetic and imaging biomarkers) to diagnose and classify patients, leading to tailored treatment approaches for AD (Arafah et al., 2023). Devi (2023) emphasised the importance of a tailored treatment approach on a detailed, case-by-case basis. The Lancet’s 2024 report also states that additional evidence suggests that changes to dementia risk factors are often cost-saving, even showing promising evidence of this effect among those with a genetic risk of dementia (Livingston et al., 2024).

1.6 AD Prevention and Treatment

Despite such widespread developments in the field, there remains no cure for AD (van der Flier et al., 2023). The symptoms are irreversible, and current pharmacological approaches primarily aim to slow the progression of symptoms (van der Flier et al., 2023). Importantly, according to Jessen (2019), research should focus on early disease detection and prevention. Thus, researchers often cite prevention (rather than treatment) as the best course of action.

Baumann & Karel (2013) specified that prevention falls into three main categories: primary, secondary, and tertiary prevention. Primary prevention involves stopping the disease or injury from occurring. It could include preventing exposure, altering the behaviour(s), or increasing resistance when exposed to the factors that may cause the disease (Baumann & Karel, 2013). Secondary prevention aims to reduce

the impact of disease when the pathology is already detectable and efforts to halt/slow the progress of the disease or implementing programmes or actions to avoid further disease progression; the overarching aim is to revert the person to their previous health and function and preventing long-term problems (Baumann & Karel, 2013). Finally, tertiary prevention aims to soften the impact of an ongoing illness or injury by managing long-term problems and an often-complex set of health problems/injuries with attempts to maximise or improve quality of life as much as possible, e.g., pharmaceutical intervention (Baumann & Karel, 2013).

Despite there being no cure, the UK National Institute for Health and Care Excellence (NICE) provides guidelines for dementia treatment to manage the symptoms temporarily: three acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) which are prescribed to manage mild to moderate AD, and memantine (an N-methyl-D-aspartate receptor antagonist) for moderate to severe AD (*“Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease,”* NICE, 2011). Drugs that aim to improve symptoms (e.g., cognitive performance and day-to-day functionality) have been largely unsuccessful (Yiannopoulou et al., 2019). Agents currently in clinical trials for AD are divided into three categories: symptomatic agents, disease-modifying immunotherapies, and disease-modifying small molecules (Cummings et al., 2023).

While these interventions represent a hopeful advancement in managing AD, their success ultimately depends on accurate diagnosis and effective monitoring of disease progression - tasks that advanced medical imaging techniques, such as MRI and PET scans, are uniquely equipped to support by revealing the structural and functional brain changes characteristic of AD (Passeri et al., 2022).

1.7 Medical Imaging

Medical imaging involves capturing health-related information about the human body using various energy types (Samei & Peck, 2019). This interaction between tissues and energy provides incredibly valuable insights into the body's structure and function (Samei & Peck, 2019). Hussain et al. (2022) described examples of medical imaging techniques, which include X-ray, computed tomography,

single-photon emission computed tomography, digital mammography, diagnostic sonography, PET, and MRI.

1.7.1 Brain Imaging

A definite diagnosis of AD is only possible following a neuropathologic evaluation of brain tissue, following an autopsy or a brain biopsy (McKhann et al., 1984; Caselli et al., 2017).

The post-mortem diagnostic process involves several steps. Initially, a detailed autopsy is performed, starting with the removal and preservation of the brain tissue as soon as possible after death to prevent post-mortem changes (Love, 2004). Gross examination is performed to assess any visible atrophy or other abnormalities in the brain (Woodworth et al., 2023). Histopathological analysis is then carried out, e.g., using immunohistochemical staining techniques (Mondal et al., 2023). Finally, these findings are compared to established diagnostic criteria, such as the Braak staging system for tau pathology (Braak & Braak, 1991). As well as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria (Mirra et al., 1991) for A β plaques.

Developments in *in vivo* imaging methods have revolutionised the field. *In vivo* (Latin for “within the living”) allows for the study of the brain in those at risk of AD or who fall along various clinical stages. Some brain imaging includes, but is not limited to, magnetic resonance imaging (MRI) and PET. These imaging modalities can be used to visualise and measure the neural structure, function, and accumulating pathology in both live human and animal subjects. *In vivo* is differentiated from other forms of research and their Latin expressions, e.g., *in vitro* (Latin for “in glass” [research involving isolating biological tissue away from the organism]) and *ex vivo* (Latin for “out of the living” [deceased]; Xu et al., 2021).

Brain imaging has a range of clinical utility in AD research (Kim et al., 2022). The current AD diagnostic process of live human patients falls broadly into four steps: detect, assess/differentiate, diagnose, and treat (Porsteinsson et al., 2021), whilst ruling out other conditions (some possibly reversible causes of cognitive impairment, e.g., depression and deficiencies in specific vitamins,

hormones, and electrolytes (Robinson et al., 2015). There has been a shift in the research community towards encouraging early diagnosis of AD to allow for appropriate future planning and consideration of symptomatic therapy pathways (Porsteinsson et al., 2021). Depending on the modality involved, one can measure various biomarkers at different spatial resolution scales, which will be covered in the next section.

1.7.1.1 Spatial Scales

In brain imaging, spatial scales refer to the different levels of resolution at which brain structures and functions can be observed (as reviewed by Eickhoff et al., 2018). The human brain exhibits complex, non-linear interactions across three spatial resolution scales: micro-, meso-, and macro-scales (Lawn et al., 2023). The micro-scale involves molecular processes, e.g., genetics, transcriptomics, and proteomics, that cover the morphology and dynamics of neurons within the brain (Scholtens et al., 2022). The mesoscale covers their (neurons') cytoarchitectonic arrangement. Lastly, the macro-scale captures brain network topology and architecture because of brain activity across multiple regions and networks (Lawn et al., 2023). This research project will focus on the macro-scale point of spatial resolution. PET imaging can measure pathology within the brain at this spatial resolution scale.

1.7.2.1 PET

Understanding brain activity at this macro-scale often requires advanced imaging techniques, such as PET scans, which measure physiological function using a radioactive tracer to detect typical and atypical metabolic activity (Berger, 2003). In PET, radioactive ligands are injected into the bloodstream, and the emitted gamma radiation can be captured using the PET scanner. PET uses several metrics to quantify the specific molecular target within regions of interest, with nanomolar sensitivity, e.g., the standard uptake value ratio (SUVr) - which is a “semiquantitative” measurement of the tracer uptake, normalised to a validated reference region, controlling for the individual's weight and the dose injected (outlined further in “*Clinical Radiation Oncology 4th Edition*” by Gunderson & Tepper, 2015). Additionally, the centiloid scale can be used for both amyloid and tau radiotracers - a metric aimed at

standardising measurements between research studies that have proven incredibly useful since its conception in 2015 (Salvadó et al., 2019). Centiloid values are calculated by linearly scaling the tracer measurement to give a value ranging from 0 to 100 (Salvadó et al., 2019). A value of “0” refers to the average uptake of the measured tracer comparable to a “young control”, and on the other end of the scale, a value of “100” is representative of the average uptake found among “typical AD patients at the dementia stage” (Salvadó et al., 2019).

AD pathological biomarkers (amyloid, tau, and neurodegeneration) can be measured using specifically constructed radiotracers targeting specific molecules, such as amyloid, tau, glucose, and many others.

1.7.2.1.1 A β -PET

Some examples of A β -PET radiotracers include carbon-11 tracers, such as ^{11}C -Pittsburgh compound B. It is one of the most widely used radiotracers for detecting amyloid plaques due to its high affinity and selectivity for fibrillar A β (e.g., Price et al., 2005). However, it is limited by its short half-life of approximately 20 minutes and is available only at test centres with a cyclotron (Krishnadas et al., 2021). Fluorine-18 (^{18}F) labelled radiotracers have been tested as effective at binding to A β , e.g., ^{18}F -Florbetaben (Barthel et al., 2011), ^{18}F -Flutemetamol (Nelissen et al., 2009), and ^{18}F -Florbetapir (Wong et al., 2010). These have demonstrated analogous results to ^{11}C -Pittsburgh compound B (Krishnadas et al., 2021). Compared to ^{11}C -Pittsburgh compound B, their relative strength is their longer radioactive decay half-life (e.g., ^{18}F radioisotopes are approximately 109 minutes; Wahl et al., 2011).

1.7.2.1.2 Tau-PET

Some examples of the most widely used radiotracers include ^{18}F -flortaucipir, ^{18}F -MK6240, ^{18}F -RO948, and ^{18}F -PI2620 (Groot et al., 2022). They demonstrate high-affinity binding to tau aggregates formed in AD. As a result, tau-PET provides a valuable opportunity to provide three-dimensional representations of the spatial patterns and distributions of tau pathology within live human subjects (Groot et al., 2022).

1.7.2.1.3 ^{18}F -fluorodeoxyglucose-PET

A third core radiotracer representing the [N] of AT[N] is ^{18}F -fluorodeoxyglucose-PET. ^{18}F -fluorodeoxyglucose-PET is used to measure the rate of metabolism of glucose within the brain (Mosconi et al., 2008; Ou et al., 2019) and is a marker of downstream processes suggesting neural injury and synaptic dysfunction (Sperling et al., 2011). It can also distinguish between dementia phenotypes, e.g., AD from Lewy bodies and frontotemporal lobar degeneration (Kato et al., 2016).

1.7.2.1.4 Other PET Tracers

While novel radiotracers for well-known biomarkers like amyloid and tau are increasingly available, additional radiotracers are being developed to visualise and quantify “X” in the “ATX[N]” model (Hampel, 2021). Whereby “X” may represent a variety of risk factors. Examples include targeting the translocator protein expression as a measure of neuro-inflammation (Gouilly et al., 2022), monoamine oxidase B, an enzyme involved in the oxidation of various amines, including, but not limited to, dopamine and norepinephrine (Meyer & Braga, 2022). Synaptic vesicle glycoprotein 2A PET is also used to measure synaptic density (Cai et al., 2019).

Building on the molecular insights provided by PET of the human brain *in vivo*, MRI complements this imaging modality by capturing structural and functional information, enabling a comprehensive view of both brain anatomy and brain activity.

1.7.2.2 Magnetic Resonance

To understand how magnetic resonance images are obtained, Gerber and Peterson take us a step back with their aptly titled article, “*What is an Image?*” (Gerber & Peterson, 2008). They define an image as “a two-dimensional, physical array of much smaller, two-dimensional squares or rectangles, which are elemental units of the picture called picture elements (or pixels)”. In this context, a pixel corresponds to a three-dimensional cube of brain tissue called a voxel (Gerber & Peterson, 2008). In brain imaging, a voxel is a portmanteau of ‘volume’ and ‘pixel’ and corresponds to a three-dimensional unit of volume

(Millar, 2014). John Ashburner and Karl Friston defined a voxel, in the context of neuroimaging, as a volumetric pixel representing a three-dimensional unit of measurement in brain imaging data (Ashburner & Friston, 2002). Each voxel corresponds to a small, discrete cube of brain tissue within a scanned volume, and the intensity or value assigned to a voxel reflects a particular property, such as tissue type, blood flow, or neural activity (Ashburner & Friston, 2002). Each voxel is represented by coordinates in three dimensions (x , y , and z) to convey spatial information and to allow for functional measurements, such as the level of activation of a voxel relative to other voxels in the brain (Ashburner & Friston, 2000). A single voxel obtained from an MRI or fMRI scan contains several hundred thousand neurons (Grill-Spector & Malach, 2001).

Understanding the significance of MRI naturally leads us first to explore its origins. MRI revolutionised how we study the brain's structure and function, and the processes involved in producing these images.

MRI is based on nuclear magnetic resonance, a phenomenon first observed by Isidor Rabi, who significantly contributed to understanding atomic nuclei in magnetic fields. For his pioneering work, he was awarded the Nobel Prize in Physics in 1944 (Rabi et al., 1939). The first two-dimensional image using nuclear magnetic resonance signals was by Paul Lauterbur in 1973. He successfully generated an image of water within two test tubes using a static magnetic field gradient (Lauterbur, 1973). Around the same time, Peter Mansfield (1933 - 2017) was another critical individual instrumental in the development of MRI. In 1972, Mansfield applied a magnetic field gradient to a sample of mm-thick layers of camphor (a waxy material), placed between plastic sheets, and then measured the nuclear magnetic resonance spectrum (Turner, 2017). The first MRI scan of a human body part was performed in 1977, and MRI was soon adopted for use with human subjects in the early 1980s (Edelstein et al., 1980). Both Lauterbur and Mansfield were awarded Nobel Prizes in 2003 for their significant contributions to MRI technology (Mayor, 2003).

This pioneering work laid the foundation for the advanced techniques we use today to acquire detailed images of the human body. The following section will delve into MRI physics and image acquisition, exploring their principles and the processes involved in producing these images.

The processes involved in magnetic resonance data acquisition can be explained using the parts of its name: “magnetic”, “resonance”, and “imaging”.

A textbook by McRobbie et al. (2017) describes MRI systems as typically using superconducting magnets capable of generating strong yet stable magnetic fields. To maintain their superconducting state and prevent electrical resistance, the system is cooled by liquid helium, a cryogenic cooling fluid (McRobbie et al., 2017).

The strength of the magnetic field is measured in Tesla, with one Tesla equivalent to 1000 milli-Tesla (Roguin, 2004). By comparison, the Earth’s magnetic field is approximately .05 milli-Tesla (McRobbie et al., 2017). Therefore, a typical MRI magnet with a strength of 3 Tesla produces a magnetic field roughly 60,000 times stronger than the Earth's (Smith & Webb, 2011).

Smith and Webb (2007) provide a detailed summation of the steps required for generating MRI images in their textbook *“Introduction to Medical Imaging”*. In MRI, gradients are used to create spatial variation in the magnetic field, allowing protons in different locations within the body to experience slightly different magnetic environments. The gradient fields are applied in three directions - x , y , and z - superimposed on the main static magnetic field (B_0). This causes protons in different regions of the body to precess at different frequencies because the frequency at which a proton precesses (its Larmor frequency) is directly proportional to the strength of the magnetic field it experiences. By varying the strength of the gradient fields across space, each location in the body can be assigned a unique frequency, effectively encoding spatial information. This enables the MRI system to differentiate between protons from different parts of the body based on their precession frequencies, which is crucial for creating an image. Once spatial encoding is in place, the MRI system can then selectively excite protons at specific frequencies using a radiofrequency pulse, flipping their spins and causing them to emit signals that are detected and used to reconstruct the spatial map of the body. This process allows for high-resolution imaging where each signal corresponds to a specific location based on the gradient fields and the precession frequency of the protons.

MRI relies on two key relaxation times: T_1 and T_2 . T_1 relaxation (spin-lattice relaxation) describes how protons return to their equilibrium state along the longitudinal axis (z -plane) after being disturbed

by a radio-frequency pulse. This relaxation time varies across tissues; for example, at 3 Tesla, grey matter has a longer T1 relaxation time (~1600ms) than white matter (~1100ms; Smith & Webb, 2011). In contrast, T2 relaxation (spin-spin relaxation) refers to the loss of transverse magnetisation as protons lose phase coherence in the transverse plane (*xy*-plane) after the pulse. This leads to a signal decay process known as free induction decay (Smith & Webb, 2011).

Additionally, T2* represents the apparent transverse relaxation time in MRI, incorporating both intrinsic tissue properties and magnetic field inhomogeneities (Chavhan et al., 2009). T2* is typically shorter than T2 due to additional dephasing effects from magnetic field variations (Chavhan et al., 2009).

In summary, the MRI machine is undoubtedly a triumph of technological advancement for medical research, with its achievement spanning multiple fields, including mathematics, physics, engineering, and medicine. However, MRI poses numerous technical and practical considerations, as do all imaging modalities. MRI offers reasonably high spatial and temporal resolution, enabling the measurement of brain structure and function, depending on the data acquisition method used (Logothetis, 2003; Glover, 2011). The signals converted into images rely on accurately measuring complex biological processes, which will be explained in more detail below.

1.7.2.2.1 Blood Oxygen Level Dependent Response Physiology

Neural activity is measured indirectly, via a proxy known as the blood oxygen level-dependent (BOLD) response. As neurons do not possess localised stores of glucose and oxygen, they depend on the influx of oxygenated blood to activate brain regions (Macy, 2013). Jenkinson and Chappell (2017) explained how the BOLD response is an *indirect* measurement of neural activity in that the reaction is mediated by a slow increase in localised oxygenated blood that takes approximately five seconds to reach its peak – a phenomenon referred to as the hemodynamic response function (West et al., 2018; Figure 1.4.).

The BOLD response was first described by Seiji Ogawa, who identified it as a contrast based on the paramagnetic properties of deoxyhaemoglobin in venous blood (Ogawa & Lee, 1990). This BOLD

contrast could provide real-time mapping of blood oxygenation *in vivo* in rats (Ogawa et al., 1990). Shortly after, the first human BOLD fMRI studies were conducted (e.g., Bandettini et al., 1992). The localised increase in blood flow involves a series of complex physiological processes that culminate in the measured BOLD response. When brain regions are activated, an increase in oxygenated blood flows to that region, creating a surplus of oxygen relative to the deoxygenated blood, as metabolic demand is less than the amount of available oxygenated blood (Attwell et al., 2010). The differences in magnetic properties between oxygenated (diamagnetic) and deoxygenated blood (paramagnetic) create variations in magnetic susceptibility in that region, which can be measured using MRI, as depicted by Arias et al. (2017). Typically, fMRI involves a gradient-echo echo-planar-imaging sequence that allows for rapidly collected multislice images, repeated at approximately 1 to 2 seconds, with a time echo (TE, e.g., at 30-40ms) to provide the necessary weighting to T_2^* (Ansorge & Graves, 2016).

Similarities in BOLD signals between brain regions indicate that they are functionally connected (as emphasised in a review by Friston, 2011). This project focuses on measuring functional connectivity using resting-state fMRI. However, before delving into functional connectivity, it is essential to describe structural MRI first, as it provides the foundational anatomical information necessary for interpreting and analysing functional data. Structural MRI offers detailed images of the brain's physical architecture, enabling the precise spatial localisation of functionally connected regions (Hirsch et al., 2015).

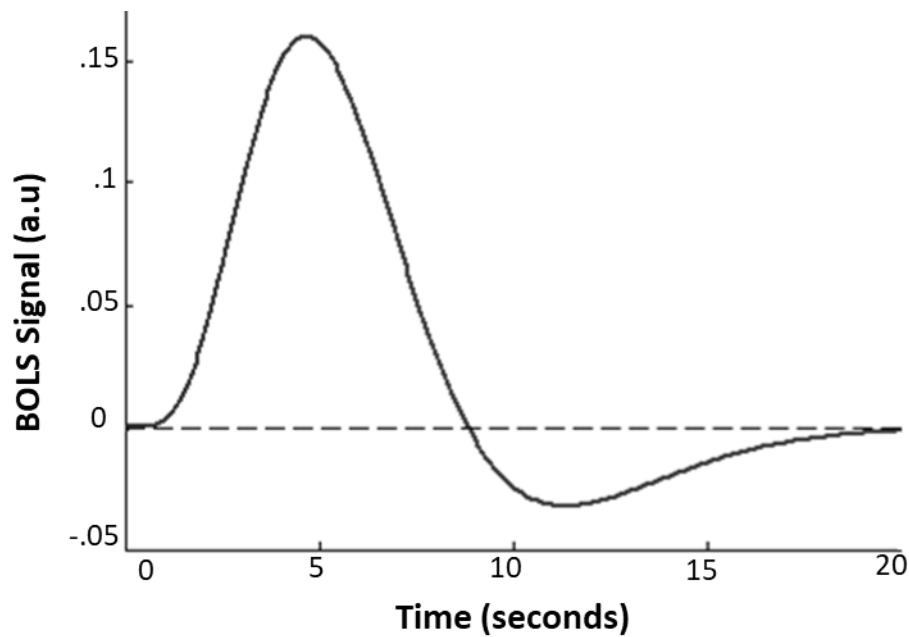


Figure 1.4. Haemodynamic response function and BOLD signal.

Note: Image adapted from West et al. (2018). BOLD = blood oxygen level dependent.

The image illustrates the haemodynamic response function.

The peak of the haemodynamic response function represents the maximum blood oxygenation level increase (BOLD signal) due to neural activation in a specific brain region (West et al., 2018). This peak typically occurs within approximately 4 to 6 seconds after the onset of neural activity, reflecting the delay in the vascular response to the initial activity (West et al., 2018).

The full-width half-maximum measures the duration of the response at half of its maximum amplitude and reflects the temporal spread of the BOLD signal, which corresponds to how long the blood flow remains elevated after the peak of neural activity (West et al., 2018).

After the peak response, the haemodynamic response function often shows a slow return to baseline, with a slight undershoot. It is due to a delayed normalisation of cerebral blood flow relative to blood volume (West et al., 2018).

A.u = arbitrary units (to depict normalised fMRI data).

1.7.2.2.2 Structural MRI

Structural MRI is a high-resolution imaging technique that provides detailed images of the brain's anatomical structures of grey matter and white matter with high clarity (Ashburner & Friston, 2000). Structural imaging can detect many conditions, including (but not limited to) lesions, stroke, hydrocephalus, neural atrophy of the grey matter, changes to white matter, and cerebrovascular disease (Chouliaras & O'Brien, 2023). Experts assess these scans visually, and quantitative methods such as voxel-based morphometry and cortical thickness measures are often used (Chouliaras & O'Brien, 2023).

A critical brain region ubiquitous in AD research and extensively studied is the hippocampus, which can be visualised and measured via T1-structural MRI. According to a review by Rao et al. (2022), the hippocampus is a widely cited brain region associated with AD due to this region's involvement in memory.

Neuroanatomically, the hippocampal formation appears as a “C-shaped” structure consisting of the “hippocampus proper” - with three significant subregions: Cornu Ammonis 1, Cornu Ammonis 2, and Cornu Ammonis 3 - and other regions including the dentate gyrus, subicular complex, and entorhinal cortex in the floor of the temporal horn of the lateral ventricle (Schultz & Engelhardt, 2014). Vast quantities of multimodal information travel through the hippocampal formation (mainly via the entorhinal cortex; Schultz & Engelhardt, 2014). The hippocampus has long been cited as instrumental in memory function and orientation (Olton et al., 1979; Lisman et al., 2017; Dahan et al., 2020).

Hippocampal atrophy, assessable through T1-weighted imaging, is also a prominent biomarker for AD. Hippocampal volume changes over one's lifespan, as exemplified in a study of over 19,700 healthy participants from the UK Biobank found that hippocampal volume decreases from mid-life (Nobis et al., 2019). In earlier studies, hippocampal volume reductions were noted in older adults with various clinical conditions, with the most significant decrease seen in those with AD (25% reduction compared to controls), followed by mixed dementia (21%), vascular dementia (11%), and normal pressure hydrocephalus (5%; Vijayakumar & Vijayakumar, 2013).

Characteristic age-related trajectories of brain volume loss occur across multiple brain regions and are not limited to the hippocampus. In healthy ageing, for instance, the temporal lobe shows accelerated atrophy around age 70, often preceded by volume loss in the hippocampus and amygdala (Fujita et al., 2023). Furthermore, volumetric measures, calculated from three-dimensional T₁-weighted images, have identified several “brain atrophy subtypes” that can be used to assess neurodegeneration and AD categorisation (Planche et al., 2020). MRI scans at baseline have been used to define and differentiate between older adults with (a) “limbic predominant atrophy”, (b) “hippocampal sparing atrophy”, (c) “typical/diffuse atrophy”, and (d) “no evidence of brain atrophy”. Those with “typical/diffuse atrophy” and “limbic predominant atrophy” were at increased risk of developing dementia later. These four brain atrophy subtypes were found to be more informative (or sensitive in predicting future dementia incidence) than less specific cortical volume measures, in which sub-categorisation of atrophy patterns could be a potential new biomarker for future studies (Planche et al., 2020).

In addition to detecting volume reductions, structural MRI can identify decreases in cortical thickness (or cortical thinning; Sattari et al., 2022). Variations in cortical thickness are one of several ways structural MRI can measure neurodegeneration. For example, research has highlighted the potentially asymmetric nature of cortical thinning in patients with AD (Roe et al., 2021). Despite its significance, asymmetrical cortical thickness is often overlooked in AD research, even though it is considered an “important feature of normal brain aging that is both shared by and accelerated in neurodegenerative AD” (Roe et al., 2021). Patients with AD were found to exhibit steeper reductions in cortical thickness within the left hemisphere, compared to the right, when measured against healthy controls, suggesting the patterns of neurodegeneration are not symmetrical - particularly in some ‘at risk’ areas, including the frontal and temporal brain regions (Roe et al., 2021). These regions are particularly vulnerable to asymmetrical loss in healthy ageing but can exhibit further (accelerated) changes in AD patients (Roe et al., 2021).

Other structural methods include measures of vascular pathology (white matter hyperintensities, lacunes, infarcts, micro- and macro-bleeds), white matter integrity via diffusion tensor imaging, blood

flow and perfusion via arterial spin labelling, to name a few (Raman et al., 2016). These imaging methods contribute to a deeper understanding of the underlying processes associated with AD.

Neuroimaging has experienced rapid advancements in data acquisition, spatial resolution, and the variety of techniques available for targeting, visualising, and measuring different aspects of the brain, as outlined in a review by Yen et al. (2023). These developments continue to enhance our understanding of the brain, including what happens to the brain during AD development and its contributing factors. However, one notable gap in the molecular and structural components of the AT[N] framework is the consideration of brain *function*, which can be measured using MRI - the same modality employed to assess neurodegeneration [N].

1.7.2.2.3 Functional MRI

MRI provides a means to measure brain structure and function at the macro-scale point of spatial resolution. This chapter will focus on functional MRI (fMRI), which can broadly be characterised into two approaches: task-based and resting-state fMRI.

1.7.2.2.3.1 Task-Based fMRI

A review by Whitten (2012) stated that event-related task-based fMRI captures participants' neural responses during specific tasks and their experiences and behaviours (Whitten, 2012). A typical task-based fMRI study may, for example, involve presenting participants with words, pictures, and sounds within the magnetic resonance scanner and measuring the evoked neural response (Whitten, 2012).

1.7.2.2.3.2 Resting-State fMRI

As the name implies, resting-state fMRI involves participants lying in a magnetic resonance scanner without exposure to specific external stimuli, distinguishing it from task-based fMRI (Lv et al., 2018). In this state, participants are considered “at rest” (Lv et al., 2018). However, “at rest” can be misleading, as the brain remains metabolically active without external tasks (Raichle & Mintun, 2006). In their

review, Raichle and Mintun (2006) emphasised that the brain's energy consumption increases by less than 5% during cognitive tasks, indicating baseline neural activity levels are high, even when the brain is not explicitly engaged in a task. From a research perspective, this is referred to as the resting state.

Resting-state fMRI marks a paradigm shift from conventional fMRI studies. However, resting-state fMRI signals are particularly noise-prone, requiring careful pre-processing and cleaning to mitigate potential pitfalls (Cole et al., 2010).

Resting-state fMRI is highly susceptible to artefacts, which can significantly confound results and lead to erroneous conclusions (Raval et al., 2021). Artefacts are defined as “a deviation of the visual integrity of an anatomic structure” (Kayacı et al., 2019) and pose significant challenges when estimating functional connectivity (Kopal et al., 2020). Artefacts arise from two primary sources: magnetic resonance hardware or subject behaviour within the scanner (Kayacı et al., 2019). To maximise data quality, effective prevention and correction strategies are paramount for distinguishing between “true” neural signals and unwanted noise (Kayacı et al., 2019).

Head motion and physiological effects are among the most common and challenging sources of artefacts in resting-state fMRI. When imaging the brain, head motion is a significant issue for the validity and reliability of results in MRI research (Hausman et al., 2022), even at the sub-mm level - termed “micro-movements” by Yan et al. (2013). Resting-state fMRI data are particularly vulnerable to the effects of motion due to the inducement of spatiotemporal changes that can lead to significant errors in functional connectivity estimates (Maknojia et al., 2019). So problematic are movements that functional connectivity estimates can be wrongly elevated, diminished, or nullified (Power et al., 2014).

Characteristic head motion patterns are evident, even among healthy individuals. For example, inferior-superior “nodding” rotational motion, often attributed to a pivot point towards the back of the neck as the subject lies within the magnetic bore in the supine position, is commonly observed (Maknojia et al., 2019). Additional motion patterns and their effects in older adults are explained below in section 1.7.2.6. The effects of head motion on resting-state fMRI data are complex and multifaceted. Movement-related effects in fMRI can broadly be divided into two classes (Friston et al., 1996):

1. In-plane motion (anterior-posterior or axial slice): Motion within a single image slice can cause variability in the recorded signal, as different brain regions may be imaged over time.

This occurs when tissue classes within the plane of the slice shift due to movement (Friston et al., 1996).

2. Between-plane motion (superior-inferior slices): Motion between slices can induce spin-history effects. This type of motion affects the magnetisation of the spins in the tissue, leading to discrepancies in the recorded signal across different slices and over time. Spin-history effects occur because the position and orientation of tissues relative to the magnetic field change, altering the MRI signal (Friston et al., 1996).

A second consequence of head motion in resting-state fMRI is the occurrence of partial volume effects. Different tissue classes - grey matter, white matter, and CSF - have different MRI signal contrast properties (Murphy & Gaillard, 2015). Partial volume effects occur most frequently when voxels are close to tissue boundaries and appear as signal fluctuations at the outer edges of the brain and the interhemispheric fissure (Maknojia et al., 2019). Moreover, technological advances in developing ultra-high magnetic field strengths (seven Tesla and above) will increase partial volume effects owing to these scanners' higher spatial resolution capabilities (Zaitsev et al., 2017). Inhomogeneities in the magnetic field can result in geometric distortions and, like partial volume effects, are more pronounced at tissue boundary borders (Togo et al., 2017). The likes of which can result in signal loss (Ojemann et al., 1997).

Lastly, head motion interacts with coil sensitivity, introducing artefacts (Faraji-Dana et al., 2016). Multi-channel receiver coils enhance signal-to-noise ratio and temporal resolution and are particularly motion-sensitive. Even minor head movements can induce blurring and other distortions in the resulting images (Hartwig et al., 2010; Faraji-Dana et al., 2016).

To address motion effects, multifaceted corrective strategies may be employed, with varying degrees of sophistication and success, to mitigate against and reduce the impact of head motion. Some examples include head restraints, behavioural intervention (instructions, education on the unintended effects of motion, mock scanners, and simulations), the adopted imaging protocol (or type, e.g., opting for more rapid two-dimensional multi-slice methods), and retrospective correction (rigid body transformations and linear regressions; Maknojia et al., 2019). Motion correction can also occur in 'real-time' (during

the data acquisition itself), by which a dynamic (as opposed to static) coordinate system is adopted (Maknojia et al., 2019).

To understand how the brain changes over AD, imaging the brain of human subjects *in vivo* is paramount. The developments of such imaging technology have arguably revolutionised the field. Imaging live subjects can be impacted by the body's physiological processes, creating notable effects on image quality (artefacts) that are important to address. For example, respirations engender changes to the magnetic field within the brain with a range of 2 to 5 hertz (Van de Moortele, 2002). The physical and unavoidable act of moving one's chest when breathing translates to head motion (e.g., Schoen et al. (2022). Furthermore, synchronised pulsivity caused by the cardiac cycle causes blood and CSF to flow throughout the brain (Womersley et al., 1955; Hermes et al., 2023). There are also region-dependent effects of noise that should be taken into consideration. For example, the brainstem suffers from poor signal-to-noise due to its physical location to bone and air pockets and being vulnerable to the effects of physiological noise (CSF flow and blood pulsivity; Brooks et al., 2013).

Careful data handling and processing are essential to mitigate against artefacts. However, resting-state fMRI data poses a high dimensionality issue (Gotts et al., 2019), as “resting-state fMRI analysis is challenging due to the massive amount of data and the need for sophisticated analysis” (Lv et al., 2018). All these raw magnetic resonance data signals are pre-processed in steps. Each step has a purpose: to maximise the data quality and remove artefacts.

However, additional (and unwanted) noise sources can pose significant problems for fMRI data analysis, leading to results with limited power and poor levels of replicability (Nieto-Castanon, 2022). The following section will cover two areas that attempt to maximise data quality and minimise potential problems before conducting statistical analyses: data pre-processing and denoising, by guidance from (Nieto-Castanon, 2022):

1. ‘Pre-processing’ is defined as a series of first steps chosen to work with structural and functional images regarding their spatial and temporal properties (Nieto-Castanon, 2022).

2. ‘Temporal variability’ in the BOLD signal in the form of physiological sources of noise (cardiac, respiratory, and other physiological factors, as well as residual motion effects not addressed entirely by pre-processing), are addressed via a series of additional steps after data pre-processing - called “denoising” (Nieto-Castanon, 2022).

An example of a resting-state fMRI pre-processing pipeline may include the following. Still, it is essential to note that steps are dependent upon the chosen software and data preprocessing algorithms:

1. Functional realignment and unwarping,
2. Slice-timing correction,
3. Outlier identification,
4. Direct segmentation and normalisation, and
5. Functional smoothing.

Each step serves a (series of) function(s) to transform the data in such a way as to maximise the data quality when creating subsequent images. However, there has yet to be a consensus on the optimal preprocessing and quality control steps when utilising resting-state fMRI (Kassinopoulos & Mitsis, 2022). There is also no “gold standard” approach for preprocessing resting-state fMRI data (De Blasi et al., 2020). This is a notable limitation of resting-state fMRI, as differences in preprocessing choices can result in different outcomes (e.g., Vergara et al., 2017).

fMRIPrep, REST, and CONN are a few examples of software that integrate preprocessing pipelines for resting-state fMRI data. CONN’s preprocessing pipeline was used for all resting-state fMRI data in this project, and it will be covered in greater detail in Chapter 3.

As described in Nieto-Castanon’s 2020 “*Handbook of functional connectivity Magnetic Resonance Imaging methods in CONN*”, even after pre-processing, the BOLD signal retains substantial noise from sources such as motion, physiological activity, and outliers, which can bias functional connectivity measurements (Nieto-Castanon, 2020). An additional set of steps – “denoising” is applied to address this. Denoising is critical in fMRI processing, as these steps aim to minimise the effects of noise and artefacts that could otherwise obscure accurate neural signals (Nieto-Castanon, 2020). Many approaches to denoising have been proposed over the past two decades. These include regressing out

respiratory and cardiac signals, sampling at multiple TEs, and employing methods utilising independent components analysis and principal components analysis (PCA) or combinations of these approaches (Beckers et al., 2023).

Effectively implementing preprocessing and denoising steps is essential, as they improve data quality and ensure that subsequent analyses accurately reflect the underlying neural activity (Luppi et al., 2024). By mitigating the presence and impact of artefacts and enhancing data integrity, researchers can map neural connections more reliably, commonly called the human “connectome”.

1.7.2.2.4 The Human Connectome and Connectomics

The human “connectome” is defined as “a comprehensive structural description of the network of elements and connections forming the human brain” (Sporns et al., 2005), and the study of the human connectome falls into the branch of “-omics” called “connectomics” (Fornito & Bullmore, 2015).

This field of connectomics aims to understand how different brain regions are interconnected and how these connections relate to cognitive processes and behaviours (Fornito & Bullmore, 2015). Connectomics can provide insights into the brain’s organisation and function, and it is becoming increasingly recognised as an essential area of study in many clinical populations, including AD and dementia (Fornito & Bullmore, 2015).

Connectomics can broadly be divided into structural connectivity, functional connectivity, and effective connectivity (Figure 1.5). This project focuses specifically on functional connectivity. I will briefly summarise these major connectivity measures before outlining each connectomics approach’s relative strengths and weaknesses.

In their 2009 review, Bullmore and Sporns described structural connectivity as the physical or anatomical connections between brain regions (Bullmore & Sporns, 2009). In contrast, functional connectivity measures the statistical associations or correlations between the activity of different brain regions, reflecting how they co-activate over time. Areas with high correlations are functionally

connected (Friston, 2011). Finally, effective connectivity refers to the causal influence one brain region exerts over another (Bullmore & Sporns, 2009; Friston, 2011).

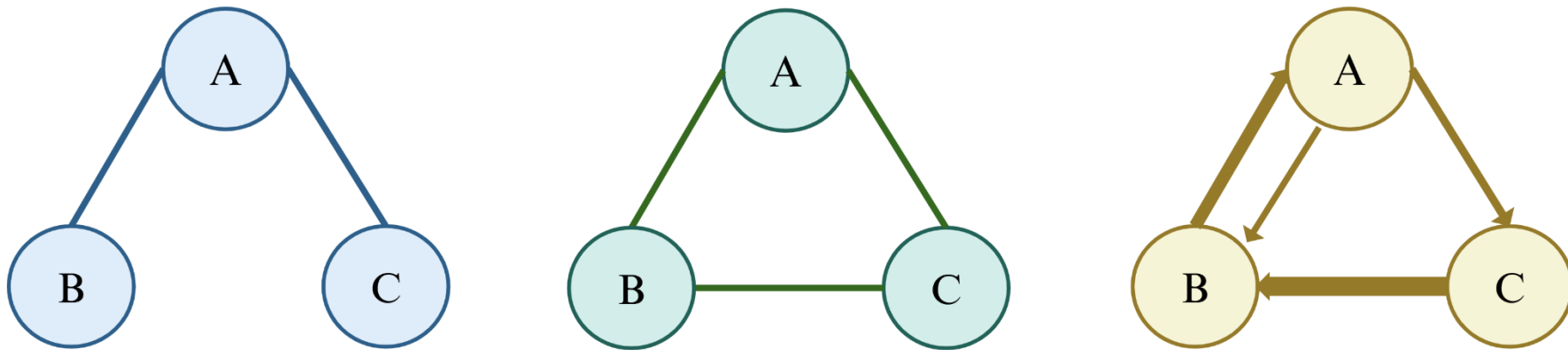


Figure 1.5. Abstraction of connectivity inferred from MRI data.

Note: Image adapted from Monachino (2019). $A - C$ = brain regions (nodes).

Left: Structural connectivity shows brain regions A being structurally connected to regions B and C *.

Middle: Functional connectivity shows undirected statistical correlations between regions $A - C$.

Right: Effective connectivity shows the direction and strengths between regions $A - C$.

*Note: anatomical/structural connectivity has a directionality, even if we cannot determine it using diffusion-weighted MR images. While the brain's anatomical connectivity might inherently have a direction (like a one-way street), diffusion-weighted MRI does not always provide enough information to conclusively determine that direction, especially in and between complex regions.

Created with BioRender.com.

Structural connectivity offers the advantage of providing a stable and anatomically consistent framework that remains relatively constant over time (Osmanlioğlu et al., 2020). Nonetheless, it has limitations, such as its low temporal resolution compared to functional connectivity (Calamante, 2019). Functional connectivity, in contrast, excels in capturing the dynamic and time-varying interactions between brain regions, reflecting how brain regions within neural networks communicate and coordinate their activity (Friston, 2011). However, resting-state fmri data are susceptible to sources of physiological noise and non-neuronal factors like cerebral vasculature (Lv et al., 2018), and show lower temporal stability compared to structural connectivity (Osmanlioğlu et al., 2020).

Finally, effective connectivity can uncover causal relationships between brain regions by providing insight into how different brain regions influence one another (Friston, 2011). Conversely, adopting this imaging method requires strong research assumptions and specific modelling choices, which can impact how the results are interpreted (Friston, 2011). Effective connectivity also requires complex modelling, posing significant analytical challenges (Friston, 2011).

This project centres on functional connectivity. The following sections will explore how functional connectivity works and introduce key examples of these measures.

1.7.2.3 Functional Connectivity Using fMRI Data

As mentioned, functional connectivity measures how our brain passes information between regions (and therefore how regions are ‘functionally connected’). This connectivity method measures the statistical dependencies between neural units that comprise a network (Sporns, 2010). These statistical dependencies can ultimately be considered ‘information’; therefore, functional connectivity measures how information is distributed and shared within a network (Sporns, 2010).

Biswal et al. (1995) conducted a pioneering study that introduced the concept of resting-state functional connectivity using fMRI. They discovered that low-frequency fluctuations in the fMRI signal during rest were correlated between functionally related brain regions, specifically demonstrating synchronised activity between the left and right primary motor cortices. This finding provided evidence that the brain maintains functional connectivity even in the absence of a task, creating a foundation for the study of intrinsic brain networks (Biswal et al., 1995). Although Biswal et al.’s work was initially dismissed as

being attributed to other signal sources, this technology has been validated. It has been widely adopted across many scientific fields and clinical populations (Biswal, 2012). As well as in AD, functional connectivity has been used in Frontotemporal Dementia and other dementia forms, as well as other neurodegenerative diseases, such as Parkinson's disease, and in several psychiatric conditions, such as depression, anxiety, obsessive-compulsive disorder, and many others (Armino & Zaharchuk, 2023). Therefore, it proves its scientific value as a flexible measure of brain function.

A review by Smitha et al. (2017) highlighted the many ways to measure functional connectivity, including seed-based connectivity, ROI-to-ROI analysis, and graph theory. Furthermore, in a systematic review and meta-analysis by Badhwar et al. (2017), they found that a common goal of functional connectivity methods in AD research is to investigate whether the connectivity within and between resting-state networks are 'altered' (or exhibit differences, for example, in comparison to healthy controls) and how they change across different AD stages - between those without overt AD symptoms, to a complete clinical AD diagnosis (Badhwar et al., 2017).

1.7.2.3.1 Functional Connectivity Measures

Functional connectivity methods can broadly be divided into methods of segregation and integration. In brain imaging, segregation represents statistical independence, while integration represents statistical *dependence* (Sporns, 2010). In network construction, segregation and integration place opposing demands regarding "local and global order" (Sporns, 2010). Moreover, segregation methods rely on task-based fMRI activity, whereas integration methods measure connectivity (Lv et al., 2018). Therefore, the latter will be of greater focus within this chapter.

Firstly, functional connectivity density is the most basic measurement of functional integration (Tomasi & Volkow, 2010). This method measures to what extent a voxel is connected but does not provide information about where (Lv et al., 2018).

Next, seed-based connectivity analysis measures functional connectivity between a “seed” (a brain region) and other brain areas. It is achieved by correlating the time series within that seed/brain region to different brain regions (Lv et al., 2018). This activation coupling between the specified seed region and other regions suggests they are involved in the same underlying functional process (Lv et al., 2018). A strength of seed-based connectivity is its simplicity in implementation, but it is limited by potential bias in requiring one to select the seed region (Lv et al., 2018). *A priori* definition of a seed location restricts the analysis to a presupposed (set of) area(s; Misaki et al., 2018).

Conversely, unlike seed-based connectivity analysis, ‘independent components analysis’ is an example of a functional connectivity method that does not rely on the *a priori* selection of seed regions aside from the selection of independent components (Lv et al., 2018). An ‘independent component’ in the context of resting-state fMRI refers to independent functional networks. It decomposes the BOLD signal into networks demonstrating synchronised BOLD activity (Lv et al., 2018).

Lastly, graph theory provides valuable insights into characterising brain network properties (Vecchio et al., 2017). One of the foundational problems in graph theory is the Seven Bridges of Königsberg, posed in the 18th century in the Russian city of Königsberg (now Kaliningrad), and is seminal to illustrating the concepts of graph theory (e.g., Kumar, 2017). Königsberg was divided by the Pregel River and connected by seven bridges (Figure 1.6.). The problem was determining whether one could walk through the city, crossing each bridge only once and returning to their starting point. Leonhard Euler, a Swiss Mathematician, addressed this problem in 1736 and laid the groundwork for modern graph theory (Euler, 1741). He represented the areas of land as “nodes” (also referred to as “vertices”) and the bridges connecting each landmass as “edges”, forming a “graph” (Figure 1.6., Euler, 1741). Euler proved that this problem was impossible to solve, as the graph did not meet the criteria for a Eulerian path, defined as a trail in a graph that visits every edge exactly once. For a Eulerian path to exist in a graph, it must have at most two nodes (or vertices) with an odd number of edges connected (Kumar, 2017).

Graph theory has numerous applications across a wide variety of fields and topics, including (but not limited to) tourism (e.g., travel movements; Park et al., 2021), understanding social networks and hierarchies (Abhishek & Hirve, 2022), and, of course, brain imaging.

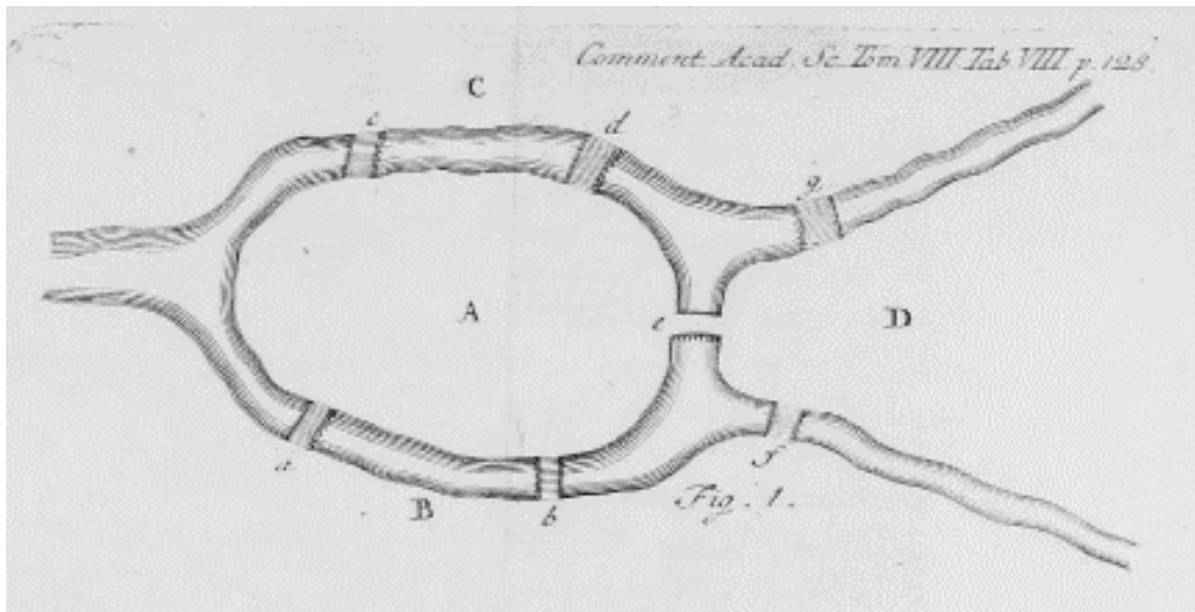


Figure 1.6. Seven Bridges of Königsberg (Euler, 1741)

Note: Image depicting the seven bridges of Königsberg (Euler, 1741) with nodes (landmasses) and edges (bridges between each landmass). *A - D* = landmasses; *a - g* = bridges.

Brain imaging shows brain networks as graphs, with nodes typically corresponding to brain regions and edges representing their relationships by physical tracts or statistical dependencies.

Functional connectivity methods provide a robust framework for modelling and analysing complex relationships inherent in large datasets. Still, multiple considerations are essential when using high-dimensional, complex sources of data or “big data”.

1.7.2.4 Big Data

Brain imaging pre-processing, denoising, and analysis are operationally demanding due to the immense complexity and computational requirements of processing and interpreting the data. Neuroimaging hence exemplifies the concept of “big data” in that it falls in line with its definition of five “Vs”: volume, variety, velocity, veracity, and value (Aiello et al., 2019): (1) ‘volume’: the amount of data within large datasets, (2) ‘variety’: data derived from multiple sources, (3) ‘velocity’: data is

generated at high speeds, (4) ‘veracity’: the data’s inherent uncertainty, and (5) ‘value’: the data’s worth. Functional neuroimaging as a big data scientific field is owed mainly to advancements in data availability, improved data infrastructure (e.g., dissemination platforms), and better analytical methods (Li et al., 2019).

1.7.2.5 Considerations of Secondary Brain Imaging Datasets

Along with these technical advances, the increased accessibility of large secondary datasets that are externally available to the public, free of charge, has significantly transformed brain imaging research. This thesis, in particular, was only possible with the availability of large imaging datasets.

A notable example of such a dataset is the Alzheimer’s Disease Neuroimaging Initiative (ADNI; Petersen et al., 2010). A search on PubMed, for instance, reveals 2923 search results for the term “ADNI” (as of the 26th of March 2024¹). By the end of 2022, a review by Veitch et al. (2024) found that ADNI clinical and ADNI imaging data had been downloaded >4.8 million and >300 million times, respectively. More than 5,000 “ADNI studies” have been published thus far (Veitch et al., 2024).

Data sharing facilitates new research by enabling teams that would otherwise be unable to access such high-dimensional datasets (Madan, 2022). This approach increases the reproducibility of brain imaging research and allows for ‘pilot’ studies to test new ideas (Madan, 2022). This is done without the substantial costs of conducting primary brain imaging data acquisition (Madan, 2022).

However, open-source neuroimaging datasets also present numerous challenges and limitations. Navigating the data organisation and working with said data (e.g., processing) can present a significant challenge (Horien et al., 2022). However, it is essential to consider working with multicentre data, as data collected across multiple sites may demonstrate potential for variability in imaging protocols and data quality (Madan, 2022).

The advent of large-scale datasets has significantly improved data accessibility, as is also the case in AD research, where large and diverse datasets are crucial for understanding age-related changes in the

¹ <https://pubmed.ncbi.nlm.nih.gov/?term=adni>

brain. Despite these exciting advancements, studies collecting imaging data from older adults, who may or may not show signs of AD and dementia, are potentially hindered by the various factors that can make imaging this population challenging.

1.7.2.6 Imaging Older Adults and Those with Disease

The specific considerations associated with the imaging population, in this case, older adults, are highly relevant to this study. Imaging this demographic necessitates careful attention to physiological and cognitive changes that occur with ageing (that may or may not be associated with AD and dementia), alongside the resulting ethical implications.

Firstly, physiological changes such as brain atrophy (characterised by a reduction in neural volume and expansion of the ventricular system) are common in ageing and complicate one's ability to differentiate between those ageing normally and those with neurodegenerative conditions, like AD and dementia (as described in a review by Fjell & Walhovd, 2010). Additionally, alterations in cerebral blood flow and vascular structures, including increased evidence of arteriosclerosis and microbleeds, can adversely affect the clarity of MRI scans, particularly in functional and susceptibility-weighted imaging (Pavuluri et al., 2024).

Next, a review by Frisoni et al. (2010) described how cognitive decline, which can arise from normal ageing or neurodegenerative diseases such as AD and dementia, can impair an older adult's ability to follow instructions during imaging procedures and data acquisition, increasing the likelihood of motion artefacts (Frisoni et al., 2010). Older adults also exhibit their distinctive patterns of head motion. For example, greater evidence of head motion was associated with age among healthy older adults (but not sex and educational levels; Hausman et al., 2022). Moreover, head motion parameters can effectively discriminate between (amnesic) MCI and AD compared to healthy controls (Haller et al., 2014). A concerning conclusion was made by Kato et al. (2021), who highlighted significant differences in head motion when comparing healthy volunteers of varying ages. They found that while there were group differences in the number of voxels with substantial variations in resting-state networks between low and high-motion groups, there were no significant differences between the low-motion groups of older

and younger adults. This suggests that head motion may significantly influence conclusions drawn about changes in brain networks associated with ageing (Kato et al., 2021), underscoring the importance of addressing and effectively managing head motion.

Lastly, ethical considerations, including the need to consider frailty to minimise discomfort (Gossner, 2022), as well as appropriate informed consent processes, are essential when imaging older adults, especially those with evidence of cognitive impairment (Higgins et al., 2023). Collaborating with healthcare professionals is therefore important when imaging older adults to consider their complex needs during MRI, especially “given the widely varying health status of elderly patients, it is crucial to tailor medical care individually” (Gossner, 2022).

Functional connectivity measures can be assessed using many methods, depending on the research questions and hypotheses being addressed. Research adopting these methods can be enriched by combining them alongside other imaging methods, called multimodal imaging (Bischof et al., 2024). For this project, combining functional connectivity measures with A β -PET and tau-PET imaging provides a powerful approach to understanding the neural underpinnings of AD. Functional connectivity analyses, particularly those utilising resting-state fMRI data, can help identify disrupted brain network interactions across the AD continuum. When integrated with PET imaging, this combination allows researchers to link group-level differences in brain functional connectivity that may be associated with underlying pathological processes.

1.8 Summary and Next Steps

AD is a complex, multifaceted, and heterogenous disease characterised by its insidious onset. Its symptoms - such as altered memory, impaired thinking, and diminished functionality - often take years to become overtly observable, leading to progressing loss of functional independence and ultimately resulting in death. The definition of AD has developed and evolved, with its most recent clinical definition emphasising the presence of abnormalities detected through various fluid and imaging biomarkers - the latter including functional and structural MRI, as well as amyloid- and tau-PET scans.

A multi-modal approach enables researchers to understand how the brain changes over AD. For instance, the combination of resting-state fMRI and PET can be utilised to assess functional connectivity and cortical and regional AD biomarker accumulation while examining their interactions. Brain regions that demonstrate functional connectivity may support each other with some shared function, such as supporting cognitive processes.

Since its inception, MRI has revolutionised our ability to visualise live human subjects, providing unprecedented insights into the brain's structure and function. The emergence of large, publicly accessible, secondary neuroimaging datasets has expanded researchers' ability to study the brain and share their findings globally.

Among various MRI data sequences, resting-state fMRI stands out because it provides valuable insight into brain function through functional connectivity analysis and enables detailed exploration of neural networks. Despite its growing popularity, it faces significant challenges, including noise and susceptibility to artefacts that compromise data quality and interpretability.

Understanding these challenges is crucial, especially in the context of neurodegenerative disorders like AD. However, a comprehensive and systematic examination of the existing literature is essential, given the complex nature of AD and how hallmark neuropathological biomarkers interact with brain function over time. This will be addressed in the next Chapter.

Chapter 2: Systematic Literature Review

2.1 Abstract

Hallmark neuropathological AD biomarkers, A β and tau, significantly impact the human functional connectome. Despite this well-established link, the methods used to measure functional connectivity vary widely, as there is no standardised approach for assessing group-level differences and changes in functional connectivity across the AD continuum.

We conducted a systematic review to provide a comprehensive and up-to-date evaluation of the evidence that (a) included groups spanning the entire AD continuum and (b) utilised measures of (i) A β -PET, (ii) tau-PET, and (iii) resting-state functional connectivity (via fMRI), either cross-sectionally or longitudinally.

A search of the PubMed database for relevant studies published up to 4th July 2024 identified 343 studies, 25 of which met the inclusion criteria after screening. While two of the 25 records showed some publication bias, most (19) achieved a Medium quality rating on the modified Newcastle Ottawa Scale. Our findings suggest that most of the 25 studies opted for a cross-sectional and data-driven design. Tau pathology emerged as being more strongly associated with disruptions in functional connectivity than A β pathology. However, both biomarkers were shown to interact in complex ways, collectively influencing resting-state functional connectivity.

Our evaluation of the current evidence indicates the need for further research to explore the relationships between A β , tau, and resting-state functional connectivity. Thereby advancing our understanding of their roles in AD development.

2.2 Introduction

Mapping the human functional connectome has a broad range of clinical applications, including AD research (Hallett et al., 2020). The functional connectome (distinct from its structural counterpart) is “the connection matrix built from the human brain”. It is measured using various imaging modalities, such as electroencephalography, magnetoencephalography, and fMRI (Hallett et al., 2020).

Changes in the functional connectome occur progressively over AD development, according to a review by Yu et al. (2021). An earlier review by Stam (2014) highlighted key patterns, such as the loss of small-world features. In the brain, “small-worldness” refers to an efficient neural network organisation that balances high local connectivity (clusters of strongly interconnected nodes) with shorter global connections, enabling both specialised processing and rapid communication across brain regions (Sporns & Honey, 2006). Another key pattern was noted by Elman et al. (2014). Their research found evidence of selective “hub” vulnerabilities (Elman et al., 2014). A “hub” is a highly connected node (e.g., a brain region) that plays a crucial role in facilitating communication between different nodes, ensuring efficient information flow within the network (Sporns et al., 2007). However, despite identifying these patterns of topological changes over AD, we have yet to determine the exact aetiological mechanisms underlying its cause. This may be attributed to inter-individual differences between patients within and between AD stages (Duara & Barker, 2022).

One major source of variance stems from neuropathological heterogeneity, particularly the differential impact of pathological biomarkers such as A β and tau (Duara & Barker, 2022). To better understand the complex relationships among A β , tau, and functional connectivity, we conducted a systematic literature review of cohort studies to evaluate the current evidence.

2.3 Materials and Methods

2.3.1 Search Strategy

The primary objective of this review was to explore broad themes found within the current research landscape of studies combining A β -PET and tau-PET to measure and quantify the cortical and regional burden of A β and tau alongside resting-state fMRI to measure functional connectivity. To achieve this, I searched the PubMed database until 4 July 2024 for eligible studies.

A targeted Boolean search strategy was employed using the following search terms:

(“Functional connectivity” AND “Alzheimer’s disease”) AND (“amyloid” OR “tau”)

2.3.2 Study Selection and Inclusion Criteria

A comprehensive list of inclusion and exclusion criteria during the screening of potentially eligible studies included the following:

Inclusion Criteria:

- **Participants:** The included studies focused on individuals across the AD continuum. Researchers used various diagnostic categories and terminologies, including (but not limited to) preclinical AD, early-stage and late-stage MCI, mild, moderate, and severe AD, AD dementia, and AD and related dementias.
- **No Cognitive Impairment and Normal Ageing:** Studies involving cognitively normal (CN) older adults and those exhibiting typical ageing were also considered.
- **Age Group:** Participants were required to be 60 or older.
- **Comorbid Conditions:** Studies were included if they involved participants along the AD continuum who also had evidence of other clinical conditions (e.g., epilepsy, diabetes, depression, etc.).
- **Functional Connectivity and Functional Connectivity Measures:** In accordance with the aims of this review, we focused on studies that used resting-state fMRI to measure functional

connectivity. Furthermore, studies that measured either static-functional connectivity or dynamic-functional connectivity measures were also included.

- **Additional Measures:** Studies that included other measures (e.g., structural connectivity using diffusion tensor imaging) along with resting-state functional connectivity were included.
- **A β and Tau Measurement(s):** Studies were included if they referenced the collection of A β AND tau via PET. This could consist of cortical biomarker burden and regional measures of these biomarkers.
- **Time Frame:** All results were included in preliminary screening regardless of publication date.
- **Spatial Resolution:** Studies were included that focused on measuring functional connectivity at the macro-scale point of spatial resolution.

Exclusion Criteria:

- **Imaging Modalities Chosen:** Studies were excluded if they (a) used only A β -PET or only tau-PET, (b) relied solely on CSF measures, or (c) combined CSF measures with either A β -PET or tau-PET. These exclusions were made to ensure alignment with the methodological framework of this thesis.
- **Other Forms of Dementia:** Studies that focused on other forms of dementia (and not AD), such as frontotemporal dementia, vascular dementia, dementia with Lewy bodies, etc., were excluded.
- **Down Syndrome:** Studies involving participants with Down syndrome, regardless of age.
- **Ex Vivo, In Vitro, and Non-human Studies:** Excluded studies include ex vivo research, studies involving only cells, those limited to computational modelling, and those involving non-human species (such as knockout mice or rat models).
- **Alternative Connectivity Measures:** Studies that measured functional connectivity through other methods (and not using resting-state fMRI), such as task-based fMRI, electroencephalogram, magnetoencephalography, or functional near-infrared spectroscopy.

Furthermore, studies that exclusively measured connectivity that was not functional, such as structural and effective connectivity.

- Age: Studies involving human subjects below the age of 60 years.
- Reviews and Commentary Articles: Systematic and narrative reviews, meta-analyses, book chapters, commentaries, and bibliometric analyses were excluded.
- Lack of A β and Tau Measures: Studies that did not include any measures of A β and tau were excluded.
- Spatial Resolution: Functional connectivity measured exclusively at the micro- or mesoscale level of the spatial resolution was excluded.

2.3.3 Data Extraction

The following data was extracted from each study: first author, date, design ([a]cross-sectional or longitudinal, and [b] data-driven or hypothesis-driven approach[s]), population(s), functional connectivity measure(s), and a summary of the pertinent findings based on our research interests.

2.3.4 Study Quality Assessment

Study quality was assessed using the modified Newcastle Ottawa Scale, which rates studies according to selection, comparability, and outcome assessment (Wells et al., n.d.). This specific version of the modified Newcastle Ottawa Scale gave a total score range from 0 to 8 instead of 0 to 9 (Stang, 2010). It also addresses some limitations of the original scale, e.g., removing the measure of representativeness and changing how confounders were scored and adjusted for (Stang, 2010). A further benefit of this chosen modified Newcastle-Ottawa Scale is that further amendments were made to promote reliability in scoring – achieved by converting a numbered star method to a binary yes/no (*“Modified Newcastle-Ottawa scale for appraisal of nonrandomized controlled studies”*, University of Pennsylvania Health System Center for Evidence-based Practice, 2016). See Table 2.1. for a summary of each record’s Newcastle Ottawa Scale score.

2.4 Results

This search initially yielded 343 results published between 2009 and 2024 (see Figure 2.1.). These articles were extracted and screened based on pre-defined inclusion and exclusion criteria, leaving 155 studies (45.19% of the original 343 results). Because the remaining records were still large, we only included studies that included both an A β -PET *and* a tau-PET. This significantly reduced the number of studies to 25 (7.29% of the original 343 results).

Lastly, the remaining records were mostly cross-sectional studies (20 out of 25 records, 80.00%) published between 2017 and 2024. They covered a range of functional connectivity measures that could broadly be defined thematically as either “data-driven” or “hypothesis-driven” (explained more in section 2.4.2).

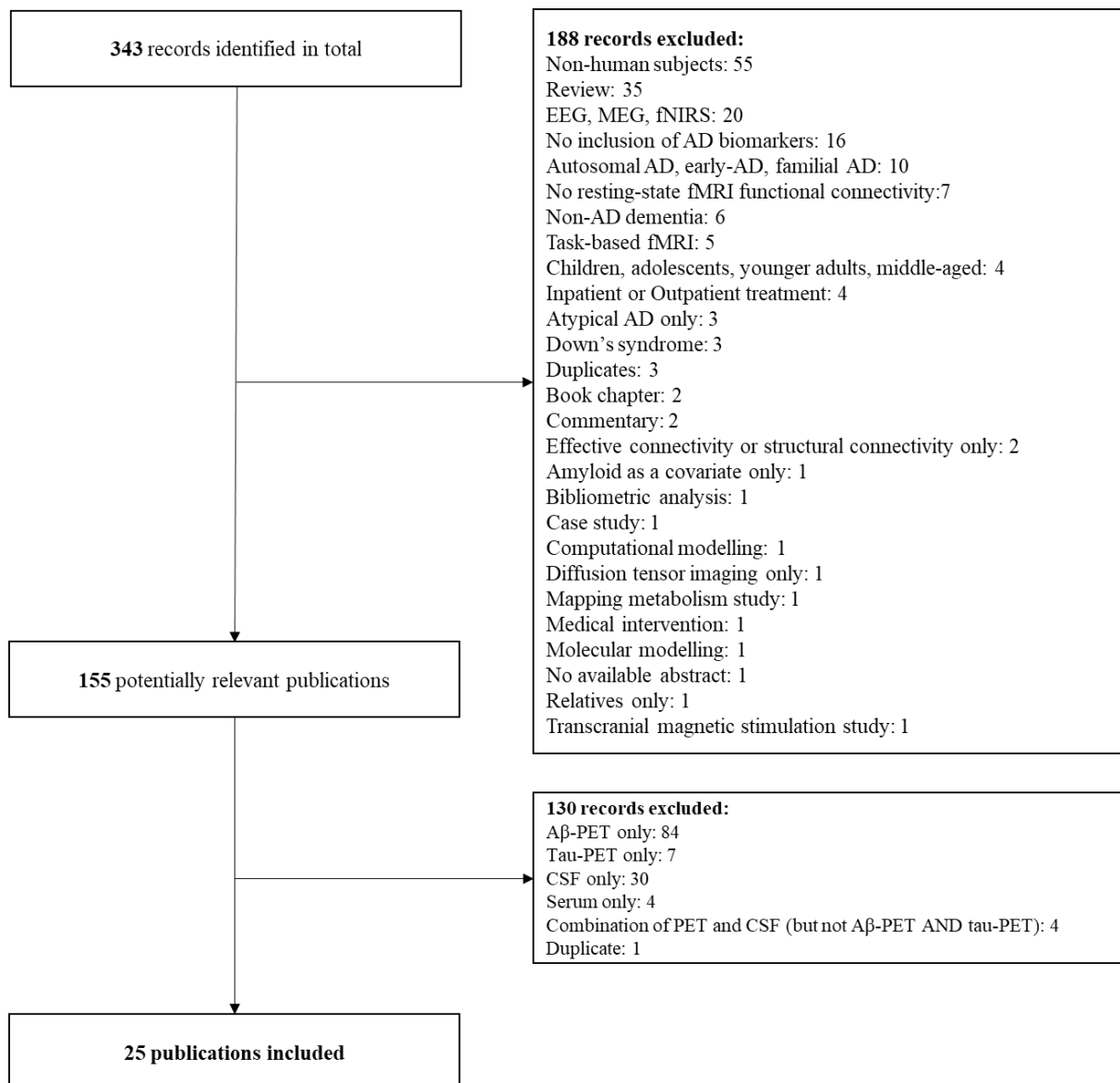


Figure 2.1. Flow chart of study selection

Note: EEG = electroencephalogram; MEG = magnetoencephalography; fNIRS = functional near-infrared spectroscopy; AD = Alzheimer's disease; fMRI = functional magnetic resonance imaging; A β = amyloid beta; PET = positron emission tomography.

2.4.1 Study Quality Assessment

By adopting the modified Newcastle Ottawa Scale, quality assessment was found to range from Low (2 out of 25 records [8.00%]) to Medium (19 out of 25 records [76.00%]) and to High (4 out of 25 records [16.00%]) (see Table 2.1.). This suggests that 80.00% of the 25 records had acceptable methodology, but some evidence of potential bias.

None of the included studies included any evidence of investigator blinding. We did not consider the lack of investigator blinding problematic, given that researchers must define contrasts at the group level to test specific hypotheses (e.g., measuring for functional connectivity between patients and controls). This process inherently requires knowledge of which group participants belong, rendering blinding impractical.

We also decided to deduct points from studies that did not control for certain confounders, mainly some form of brain volume as a covariate of no interest. This was one of the reasons that many records were demoted from “High” to “Medium”. Regardless, we believed that brain volume is an important covariate for studies of this nature to warrant this criterion. Studies that controlled for confounders mainly controlled for age and sex. However, not controlling for brain volume may mean that results are confounded by structural atrophy (Voevodskaya et al., 2014), individual differences in brain size (O’Brien et al., 2011), and sex differences in brain structure (not accounted for when controlling for sex alone; Forde et al., 2020).

Furthermore, eight studies showed no evidence of controlling for multiple tests (e.g., using a Bonferroni correction; Bonferroni, 1936), which could introduce an additional source of bias (Bennett et al., 2009) by increasing the risk of making at least one type I error (false positive; Herzog et al., 2019).

Table 2.1. Modified Newcastle Ottawa scale study quality assessment rating scores

	Study	Domain							Score	
		Study Groups	Attrition	Exposure Measure	Outcome Measure	Investigators Blinded	Confounders Identified	Statistical Adjustment		
1	Abuwarda et al. (2024)	✓	✓	✓	✓	✗	✓	✓	7	High
2	Adams et al. (2019)	✗	✓	✗	✓	✗	✗	✓	4	Low
3	Binette et al. (2022)	✓	✓	✓	✓	✗	✗	✓	5	Medium
4	Bueichekú et al. (2024)	✓	✓	✓	✓	✗	✗	✓	5	Medium
5	Canal-Garcia et al. (2024)	✓	✓	✓	✓	✗	✗	✓	6	Medium
6	Cassady et al. (2023)	✓	✓	✓	✓	✗	✓	✗	6	Medium
7	Chen et al. (2020)	✓	✓	✓	✓	✗	✓	✗	6	Medium
8	Franzmeier et al. (2019)	✓	✓	✓	✓	✗	✗	✗	5	Medium
9	Franzmeier et al. (2020)	✓	✓	✓	✓	✗	✓	✓	7	High
10	Köbe et al. (2021)	✓	✓	✓	✓	✗	✗	✓	6	Medium
11	Lee et al. (2019)	✓	✓	✓	✓	✗	✓	✓	7	High
12	Liu et al. (2022)	✓	✓	✓	✓	✗	✗	✓	6	Medium
13	Meeker et al. (2020)	✓	✓	✓	✓	✗	✗	✗	5	Medium
14	Mijalkov et al. (2023)	✓	✓	✓	✓	✗	✗	✓	6	Medium
15	Millar et al. (2023)	✓	✓	✓	✓	✗	✗	✓	6	Medium
16	Neitzel et al. (2019)	✓	✓	✓	✓	✗	✗	✗	5	Medium
17	Ossenkoppele et al. (2019)	✗	✓	✓	✓	✗	✓	✗	5	Medium
18	Quevenco et al. (2020)	✓	✓	✓	✓	✗	✗	✓	6	Medium
19	Rubinski et al. (2022)	✓	✓	✓	✓	✗	✗	✓	6	Medium
20	Schultz et al. (2017)	✓	✓	✓	✓	✗	✗	✓	6	Medium
21	Schumacher et al. (2021)	✓	✓	✓	✓	✗	✗	✓	6	Medium
22	Sepulcre et al. (2017)	✗	✓	✓	✓	✗	✗	✓	4	Low
23	Zeng et al. (2022)	✓	✓	✓	✓	✗	✓	✓	7	High
24	Zheng et al. (2023)	✓	✓	✓	✓	✗	✗	✗	5	Medium
25	Zhou & Bai (2017)	✓	✓	✓	✓	✗	✗	✗	5	Medium

Notes. Red = “no” (the study did not meet the criteria for the domain); Green = “yes” (the study did meet the criteria for the domain). A score of 0 to 2 = very low quality; 3 to 4 = low quality; 5 to 6 = moderate quality; and 7 to 8 = high quality.

2.4.2 Measures of Functional Connectivity

The 25 studies included in this review employed a range of methodologies to assess functional connectivity. These can be broadly categorised as follows:

- **Data-Driven, Whole-Brain Approach:** This method involves analysing the entire brain without prior assumptions, using techniques that capture comprehensive, unbiased data patterns across all brain regions. Typically, unbiased and exploratory, these methods leverage data-driven algorithms to identify patterns of interest (e.g., whole-brain connectivity analyses, machine learning; Calhoun, 2018).
- **Hypothesis-Driven, Region-Specific Approach:** This method focuses on pre-selected brain regions or networks based on prior knowledge, assumptions, or specific hypotheses (e.g., Li et al., 2023). It involves targeted analysis of predefined areas (e.g., extracting “seed” regions for seed-based connectivity analysis, opting to focus on a singular brain network, such as the Default Mode; Li et al., 2023).

2.4.2.1 Data-Driven, Whole-Brain Approach

See Table 2.2 for a broad-level overview of the 25 records included in this Chapter.

Of the 25 records, 14 utilised data-driven approaches to measure functional connectivity. For instance, Meeker et al. (2020) examined global resting-state functional connectivity signature differences between CN African American and White participants. Similarly, Abuwarda et al. (2024) employed a specific whole-brain measure known as “connectome-based predictive modeling” to identify brain networks linked to A β and tau burden among cognitively unimpaired older adults. This approach treated functional connectivity matrices as predictors and A β and tau measures as outcomes (Abuwarda et al., 2024). Then, correlating the strength of each brain connection with these biomarkers to produce a single correlation matrix (Abuwarda et al., 2024).

Expanding on the use of data-driven approaches, Canal-Garcia et al. (2024) measured dynamic (rather than static) functional connectivity by defining brain nodes across 200 cortical regions grouped into

seven resting-state networks, analysing group levels functional connectivity differences between CN A β -, CN A β +, MCI A β +, and AD A β + participants.

Additionally, Franzmeier et al. (2019) used an atlas-based method, measuring functional connectivity across the Schaefer atlas (Schaefer et al., 2018) to compare connectivity patterns between CN A β -, AD (A β +), and participants with vascular cognitive impairment due to small vessel disease. Similarly, Franzmeier and colleagues used this same atlas-based approach again for their 2020 study (Franzmeier et al., 2020).

Further leveraging whole-brain analyses, Köbe et al. (2021) again applied a Schaefer parcellation scheme involving predefined regions classified into seven functional networks. In a related study, Millar et al. (2023) investigated the “brain age gap” (the difference between one’s appeared brain age and chronological age) by testing models based on functional connectivity, structural connectivity, and a combined multimodal approach. They used a 300×300 Fisher-transformed Pearson correlation matrix to predict brain age differences among CN and cognitively impaired participants.

Binette et al. (2022) developed a template matrix of 200 regions from unimpaired participants with low A β - and tau-PET binding, correlating tau-PET rates of change with functional connectivity to tau epicentres. Focusing on pairwise connectivity, Zheng et al. (2023) conducted ROI-to-ROI analyses using the Schaefer atlas to compare A β + participants within the AD spectrum, A β - participants, and healthy controls, while Bueichekú et al. (2024) combined whole-brain voxel-wise and ROI-to-ROI approaches.

Sepulcre et al. (2017) adopted a different approach, focusing on “local and distant connectivity” analysis (compiling a series of functional connectivity maps at the local and distributed levels) to compare functional connectivity between CN older adults and younger adults.

In contrast, Lee et al. (2019) used graph theory metrics, such as global efficiency (how efficiently the information can be exchanged across a network; Ek et al., 2015) and clustering coefficients (the extent to which nodes within a graph tend to cluster together; Li et al., 2016), to assess brain networks defined by the 116 “Automated Anatomical Labelling 3” (AAL) atlas (Rolls et al., 2020) regions across normal ageing, MCI, and AD groups. Similarly, Mijalkov et al. (2023) adopted the same graph theory

metrics to compare topological characteristics across the whole brain by comparing these patterns between CN, MCI, and AD dementia participants with or without cortical A β burden.

2.4.2.2 Hypothesis-Driven, Region-Specific Approach

The remaining 11 studies adopted a more hypothesis-driven, region-specific approach, focusing on selected brain areas, networks, or specific regions of interest. These approaches ranged from examining large cortical areas (e.g., global left frontal cortex) to isolating particular resting-state networks (e.g., Default Mode) or individual brain regions.

For instance, Neitzel et al. (2019) computed global left frontal cortex functional connectivity - a marker of cognitive reserve (Cole et al., 2012) - for each participant (either A β + CN and A β + MCI). This was achieved by using the left frontal cortex as a “seed” region and calculating its functional connectivity with all other brain voxels. Additionally, they examined the frontoparietal control network, a major functional hub connected to the left frontal cortex (Cole et al., 2012). Similarly, Schultz et al. (2017) analysed network-level functional connectivity across several networks, including the Default Mode, Salience, Dorsal Attention, and Frontoparietal Control networks, comparing A β + and A β - CN older adults.

Some studies focused on isolating specific brain networks. For example, Cassady et al. (2023) targeted the episodic memory network to assess functional connectivity at rest and during an object-scene mnemonic discrimination task, comparing young and older adults. Other studies examined functional connectivity between the anterolateral entorhinal cortex and the anterior-temporal and posterior-medial memory networks over a follow-up of 2.80 years (Chen et al., 2020) or focused on Default Mode network functional connectivity among normal controls, MCI patients, and early AD patients (Zhou & Bai, 2017).

Several researchers opted for *a priori* “seed” regions. For example, Ossenkoppele et al. (2019) used a “syndrome-specific epicenters” approach. They targeted brain regions commonly affected by AD,

such as the left superior temporal gyrus and left posterior cingulate cortex. They compared the functional connectivity patterns of these regions between AD patients and young adult controls.

Two studies focused on the basal forebrain cholinergic system, specifically targeting the Ch1-3 and Ch4 subregions as “seeds” for seed-based connectivity analysis. Liu et al. (2022) explored functional connectivity from these regions in CN and MCI participants with different combinations of APOE ϵ 2 and ϵ 3 alleles, while Zeng et al. (2022) extended this analysis to “cognitively intact” older adults classified by their A β and tau profiles.

Adams et al. (2019) also utilised seed-based connectivity analysis with sub-regions of the entorhinal cortex (anterolateral and posteromedial portions). They measured functional connectivity from these regions to the rest of the brain. They hypothesised that functional connectivity patterns from the anterolateral portion, the area of earliest tau deposition, would more accurately predict cortical tau accumulation compared to the posteromedial portion.

Finally, Quevenco et al. (2020) created seed maps for the posterior cingulate and precuneus sub-regions of the Default Mode network to analyse differences in CN older adults stratified by APOE ϵ 4 status.

Table 2.2. Summaries of research meeting all inclusion criteria

Study	Date	Design	Population(s)	Functional Connectivity Measure(s)	A β and Tau Measures	Brief Summary of Relevant Findings
Abuwarda et al.	2024	Cross-sectional Data-Driven, Whole-Brain Approach	1,491 cognitively unimpaired adults, with 394 having available tau-PET images, and included 51 healthy controls and 342 A β + individuals. The Human Connectome Project-Aging comprised 689 healthy subjects (36 - 100).	Connectome-based predictive modelling to assess whole-brain functional connectivity.	A β -PET measures both cortical and regional A β burden, and tau-PET measures regional levels of tau.	Functional connectivity predicted tau-PET more effectively than A β -PET. Linear relationships were evident between functional connectivity and tau.
Adams et al.	2019	Cross-sectional Hypothesis-Driven, Region-Specific Approach	55 young adults and 123 CN older adults.	Seed-based connectivity analysis was used to assess the potential differences in functional connectivity, with the anterolateral and posteromedial entorhinal cortex portions being used as seeds.	Cortical A β load was used to determine A β status (A β - and A β +) via PET and tau-PET to measure cortical tau load.	Tau was more prominently deposited in cortical areas connected to the anterolateral entorhinal cortex than those connected to the posteromedial entorhinal cortex or non-functionally connected regions. Greater functional connectivity to the anterior region correlated with higher tau deposition. Relationships between functional connectivity and tau levels were observed regardless of A β levels, though these associations were amplified when A β was present.

Binette et al.	2022	Longitudinal	119 participants consisting of those who were defined as cognitively unimpaired and those with MCI.	Functional connectivity related to tau epicentres.	A mixture of A β -PET, tau-PET and CSF tau measures depending on data availability across two datasets.	The study proposes a two-stage model that reconciles the early and late stages of AD pathology:
		Data-Driven, Whole-Brain Approach		Functional connectivity matrices were created according to the Schaefer atlas.		• <i>Early Stage</i>: The model suggests that an initial increase in Aβ fibrils leads to elevated soluble p-tau concentrations. • <i>Later Stage</i>: Once a threshold of tau aggregates is reached, local self-replication and accumulation of misfolded tau become dominant.
Bueichekú et al.	2024	Cross-sectional	335 individuals for A β -PET and tau-PET imaging and 713 individuals for resting-state fMRI from the A4 and LEARN studies.	Combination of whole-brain voxel-wise and ROI-to-ROI analyses.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Individuals with unawareness of memory decline exhibited significantly higher A β and tau burden within midline regions of the Default Mode network compared to those who were measured as being more aware of memory decline, those who complained about memory decline, and healthy control group.
		Data-Driven, Whole-Brain Approach (This was followed with ROI analyses)				A distinctive pattern of hyper functional connectivity in the medial anterior prefrontal cortex and posterior occipitoparietal regions marked unawareness of one's memory decline. These patterns were co-located with both Aβ and tau deposition.

Canal-Garcia et al.	2024	Cross-sectional Data-Driven, Whole-Brain Approach	CN A β - ($n = 86$), CN A β + ($n = 37$), MCI A β + ($n = 34$), AD A β + ($n = 22$).	Dynamic Multilayer Network Analysis was employed to analyse dynamic functional connectivity.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Temporal multilayer network measures successfully differentiated between AD stages, especially early on for those at early—preclinical—stages. This ability to differentiate between stages surpassed more traditional risk factors (age, sex, and APOE $\epsilon 4$ status).
Cassady et al.	2023	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Young adults (13 males, 11 females) and CN older adults (18 males, 31 females).	Functional connectivity similarity between rest and an object-scene mnemonic discrimination task. Episodic memory network parcellation.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Lower functional connectivity similarity in the Episodic Memory network correlated with higher tau levels and poorer performance on object trials. This suggests that AD pathology (especially tau) is linked to a less stable functional architecture within memory networks.
Chen et al.	2020	Longitudinal Hypothesis-Driven, Region-Specific Approach	124 CN older adults (74 females, 50 males) followed for an average of 2.80 years.	Functional connectivity between the anterolateral entorhinal cortex and the anterior-temporal and posterior-medial memory networks over a follow-up of 2.80 years.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Tau, facilitated by A β , was found to spread from the entorhinal cortex to cortical regions linked to the entorhinal cortex. This relationship was found to impact memory in early AD stages. particularly
Franzmeier et al.	2019	Cross-sectional Data-Driven, Whole-Brain Approach	Fifty-five elderly participants (CN A β -), 50 AD (A β +), and 36 participants with vascular cognitive impairment (A β -) due to small vessel disease.	“Atlas-based” (whole brain) functional connectivity across 400 regions of interest.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Higher functional connectivity between regions was associated with higher covariance in tau-PET binding.

Franzmeier et al.	2020	Longitudinal Data-Driven, Whole-Brain Approach	Fifty-three A β biomarker defined AD participants (from the ADNI study), 41 AD subjects (from the BioFINDER study), 28 A β - healthy controls (ADNI), and 16 controls (BioFINDER).	Resting-state fMRI assessed functional connectivity between 400 ROIs.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Higher functional connectivity in AD was associated with faster tau accumulation in corresponding ROIs.
Köbe et al.	2021	Longitudinal Data-Driven, Whole-Brain Approach	Two hundred forty-seven cognitively unimpaired individuals with a family history of sporadic AD.	Global (whole-brain) functional connectivity.	A β -PET for determining A β status and tau-PET for regional measures of tau load.	Global functional connectivity increased over time. A β and tau were not associated with functional connectivity changes over time.
Lee et al.	2019	Cross-sectional Data-Driven, Whole-Brain Approach	Eighty-seven subjects: 21 with AD, 32 with MCI, 34 with normal ageing.	Network analysis (across 116 AAL regions) using graph theory.	The key analyses assessed the degree of A β and tau (as quantitative variables) were measured (as opposed to status).	Network analysis revealed that higher cognitive reserve was associated with better global efficiency and local network properties, particularly in the right middle-temporal pole.

Liu et al.	2022	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Sixty MCI participants with APOE $\epsilon 3 / \epsilon 3$, 18 MCI participants with APOE $\epsilon 2 / \epsilon 3$, 73 CN subjects with APOE $\epsilon 3 / \epsilon 3$, and 36 CN subjects with APOE $\epsilon 2 / \epsilon 3$.	Basal forebrain cholinergic system functional connectivity. Subregions were used as “seeds” for seed-based connectivity analysis.	Tau-PET measured regional burden across all Braak stages. Participants' A β burden was measured by PET and was estimated using a summary whole cerebrum SUVR.	An interaction effect on functional connectivity was found between the various regions. Right Ch4—to—left insula functional connectivity was associated with early tau deposition among all subjects and APOE2 $\epsilon 2$ carriers. No correlation was found between imaging metrics and A β burden, but functional connectivity metrics were associated with cognitive performance in all subjects and APOE $\epsilon 2$ carriers.
Meeker et al.	2020	Cross-sectional Data-Driven, Whole-Brain Approach	CN African American ($n = 131$) and CN White ($n = 685$) adults aged 45 and older.	Global resting-state functional connectivity signature.	Centiloid (total cortical A β burden) and tau-PET (tauopathy burden [the arithmetic mean of four regions: amygdala, entorhinal cortex, inferior temporal region, and lateral occipital regions]) were measured.	No racial differences were observed for A β , tau levels, or resting-state functional connectivity.
Mijalkov et al.	2023	Cross-sectional	One hundred sixty-six individuals: A β - and A β + CN participants,	Whole-brain functional connectivity was assessed through clustering	Global/cortical via A β -PET and tau Braak stages using tau-PET.	Non-linear differences in global efficiency were observed, especially in the early stages of AD.

		Data-Driven, Whole-Brain Approach	those with MCI, and those with AD dementia.	coefficient and global efficiency.		Both global efficiency and clustering coefficient showed quadratic associations with A β / tau pathology.
Millar et al.	2023	Cross-sectional	Training Sample: 390 A β -, CN (CN / A β -). Independent Test Samples: 144 CN / A β - participants, 154 A β +, 154 cognitively impaired participants (with CDR > 0).	Brain Age Prediction Models - including functional connectivity models.	A β positivity via PET and tauopathy (mean of bilateral amygdala, entorhinal, inferior temporal, and lateral occipital regions).	Combining structural and functional connectivity MRI improved brain age prediction.
		Data-Driven, Whole-Brain Approach		Functional connectivity measured as a 300 x 300 matrix		The functional connectivity brain age gap was significantly reduced among CN A β + participants compared to CN A β -).
Neitzel et al.	2019	Cross-sectional		Global left frontal cortex functional connectivity (a substrate of cognitive reserve) was computed for each participant as the average functional connectivity between the left frontal cortex (as a seed region) and all other remaining voxels.		Higher entorhinal tau-PET levels were associated with poorer delayed free recall performance.
		Hypothesis-Driven, Region-Specific Approach	One hundred twenty-five elderly participants from the ADNI study: 82 CN (27 A β +) and 43 participants with amnesic MCI (15 A β +).	The frontoparietal control network was also measured (due to it being a major functional hub of the left frontal cortex).	A β -PET for determining A β status and tau-PET for regional measures of tau load – entorhinal cortex only.	A significant interaction was found between functional connectivity and entorhinal tau PET levels. A significant global left frontal cortex function connectivity $\times$ entorhinal tau-PET interaction was found.

Ossenkoppele et al.	2019	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Sixty-three participants with AD and 1,000 young adults.	“syndrome-specific epicenters” approach: targeting brain regions that are often affected by neurodegenerative diseases, such as AD.	Aβ-PET and tau-PET covariance patterns with functional connectivity maps.	Strong convergence between tau covariance patterns and intrinsic functional connectivity maps was observed. By comparison, the topography of Aβ was less linked to networks. This suggests that tau pathology follows functional networks in the brain. In contrast, Aβ patterns were more diffuse.
Quevenco et al.	2020	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Fifty-seven cognitively unimpaired older adults.	Seed-maps of the posterior cingulate and precuneus.	Local Aβ and tau load using PET.	Increased local Aβ was associated with heightened/increased functional connectivity in frontal and parietal regions. However, tau accumulation was linked to increased functional connectivity across a broader range of brain regions. A significant interaction was observed between APOE ε4 carrier status and functional connectivity. This was most evident in brain regions with elevated Aβ and tau burden/retention.
Rubinski et al.	2022	Longitudinal Data-Driven, Whole-Brain Approach	Aβ+ asymptomatic and symptomatic older adults (ADNI: $n = 275$, BioFINDER-1: $n = 102$).	Whole brain ROI-to-ROI functional connectivity using a 200 ROI brain-parcellation atlas.	Aβ-PET for determining Aβ status and tau-PET for regional measures of tau load.	Myelin may protect functionally connected brain areas from tau accumulation, offering insights into regional tau vulnerability in AD.

Schultz et al.	2017	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Ninety-one participants were all CN at baseline.	Functional connectivity in four resting-state networks (Default Mode, Salience, Dorsal Attention, and Frontoparietal control).	Global cortical A β -PET and regional tau in the entorhinal, inferior temporal, and inferior parietal cortex.	A β + participants exhibited increased functional connectivity in the Default Mode and Salience networks at low tau levels. This transitioned to decreased functional connectivity when tau was found to be elevated tau. Together, this suggests that a hyperconnectivity phase is followed by hypoconnectivity at the preclinical AD.
Schumacher et al.	2021	Cross-sectional Hypothesis-Driven, Region-Specific Approach	One hundred fifty-two total participants, including 27 dementia with Lewy bodies participants, 26 AD participants, and 99 cognitively unimpaired controls.	Network-level functional connectivity (Schaefer atlas was used to group brain regions into seven large-scale networks). Default Mode, Dorsal Attention, Limbic, Ventral Attention, Somatomotor, and Visual networks.	A β -PET for A β status and regional tau levels for measures of network-specificity tau uptake.	Higher functional connectivity was associated with tau covariance across all groups. Functional connectivity to tau hotspots (e.g., inferior/medial temporal cortex) correlated with increased tau, while functional connectivity to tau cold spots (e.g., sensory-motor cortex) was associated with lower tau.
Sepulcre et al.	2017	Cross-sectional Data-Driven, Whole-Brain Approach	Thirty-nine CN older adults and 39 CN young adults.	Whole-brain functional connectivity analysis: “local and distant connectivity” analysis.	A β -PET and tau-PET to measure cortical spatial relationships.	Most frequent associations: • A negative association was found between tau and functional connectivity. • A positive association was then observed between Aβ and functional connectivity.

Zeng et al.	2022	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Two hundred and twenty-nine “cognitively intact” participants. One hundred seventy-three subjects were classified into three groups based on the “A / T” profile: A- / T -, A+ / T-, A+ / T+ (excluding A- / T+).	Seed-based connectivity analysis of basal forebrain subregions (cholinergic neurons 1 to 3 and 4) with whole-brain voxels.	Compiling average maps of tau and A β deposits and for A β and tau profiling.	Increased functional connectivity was observed between the right Ch4 and bilateral amygdala in AD continuum groups. Functional connectivity values effectively distinguished the A- / T-group from the A+ / T- and A+ / T+ groups. Enhanced Ch4-to-amygdala functional connectivity correlated with higher A β and tau levels.
Zheng et al.	2023	Cross-sectional Data-Driven, Whole-Brain Approach	Six hundred eighty-five participants (395 A β + participants within the AD spectrum, 290 A β -controls, and 1,000 healthy controls).	Pairwise ROI-to-ROI functional connectivity for all pairs in the Schaefer atlas.	A β -PET for A β status and A β z-scores, and regional tau scores.	Functional connectivity alone explained 21.80% to 39.20% of the variance in tau-PET ROI values. Combining all predictors (adding A β and gene expression) significantly improved the amount of variability explained.
Zhou & Bai	2017	Cross-sectional Hypothesis-Driven, Region-Specific Approach	Eighteen normal controls, 24 MCI patients, and three patients with early AD.	Functional connectivity of the Default Mode network.	Regional A β and tau values.	Significant correlations were observed between tau and MRI metrics, including functional connectivity.

Notes. CN = cognitively normal; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease; A β +/- = amyloid beta positive/negative; ROI = region of interest; PET = positron emission tomography; (f)MRI = (functional) magnetic resonance imaging; A / T = amyloid/tau; CDR = Clinical Dementia Rating; APOE ϵ 4 = Apolipoprotein E ϵ 4; ADNI = Alzheimer's Disease Neuroimaging Initiative; SUVR = standardised uptake value ratio; AAL = Automated Anatomical Labelling (atlas).

2.5 Discussion

This review included 25 studies (from an initial pool of 343), all utilising both A β -PET and tau-PET imaging measures alongside resting-state fMRI to investigate functional connectivity. The following sections will provide some high-level themes and key findings related to the interplay between functional connectivity and these AD biomarkers.

2.5.1 Functional Connectivity and AD Biomarkers

Although A β burden is a hallmark biomarker of AD, its relationship with functional connectivity is more diffuse and less robust than tau (Ossenkoppele et al., 2019). However, the presence of A β can amplify tau's effects on network connectivity, suggesting that these biomarkers interact (Adams et al., 2019; Chen et al., 2020). Abuwarda et al. (2024) also found that functional connectivity metrics are more strongly associated with tau pathology than with A β , indicating that tau may have a closer link to network disruptions during AD development.

Both data-driven approaches (e.g., Abuwarda et al., 2024) and hypothesis-driven approaches (e.g., Adams et al., 2019) consistently found that higher tau deposition correlated with increased or altered functional connectivity patterns. In addition, Abuwarda et al. (2024) found that functional connectivity better predicted tau-PET outcomes much more effectively than A β -PET, suggesting that tau's impact on functional connectivity may be more pronounced. Together, the above results align with the hypothesis that while A β may initiate earlier, tau deposition drives neurodegeneration and functional decline, particularly in memory and executive function networks (Zhang et al., 2021).

Several studies also highlighted that A β and tau affect brain networks differently. A β exhibited a more diffuse deposition pattern, often associated with increased connectivity in regions like the frontal cortex. This hyperconnectivity potentially reflects compensatory effects (e.g., Quevenco et al., 2020).

Conversely, tau deposition was more localised to memory-related areas such as the entorhinal cortex and hippocampus, which are important for cognitive function, including episodic memory (e.g., Chen et al., 2020; Cassady et al., 2023). This distinction suggests that tau pathology's spatial specificity may

make this biomarker a more direct driver of cognitive decline, particularly during the early stages of AD development, e.g., when cognitive impairment is not yet observable.

In addition to characterising biomarker relationships, functional connectivity measures demonstrated predictive value for cognitive decline. Millar et al. (2023) showed that connectivity metrics outperformed A β or tau alone in forecasting future cognitive decline and brain ageing. This finding emphasises the potential of functional connectivity as a sensitive biomarker for early detection and clinical intervention in AD (Millar et al., 2023).

2.5.2 Functional Connectivity Patterns

We identified a focal interest in the Default Mode and other memory-related networks. These networks showed variable functional connectivity patterns influenced by participants' tau and A β burden levels. For example, Schultz et al. (2017) observed an initial phase of increased functional connectivity in A β ⁺ individuals with low tau, which transitioned to decreased functional connectivity as tau increased.

Region-specific studies, such as those by Chen et al. (2020) and Cassady et al. (2023), found that functional connectivity changes were more prominent in memory-related networks and regions like the entorhinal cortex. These alterations significantly affect episodic memory performance. Moreover, several studies observed that tau preferentially accumulated in areas functionally connected to the entorhinal cortex (Adams et al., 2019) and memory-related networks (Schumacher et al., 2021). This specificity may explain why tau has a more significant impact on memory decline than A β , which shows a more diffuse pattern. The entorhinal cortex was of special interest, as it is one of the earliest sites of tau deposition (Jacobs et al., 2020).

Schumacher et al. (2021) further demonstrated that higher functional connectivity in memory-related regions (e.g., the medial temporal cortex) was associated with increased tau. Conversely, brain regions with less functional connectivity to tau hotspots (e.g., sensory-motor areas) were less affected.

Multiple studies' insights into network - and region-specific tau in these specific networks reinforce the notion that interventions targeting tau in these specific networks could be pivotal in slowing cognitive decline.

2.5.3 Included Records' Study Design and Methodological Choices

The included studies were published between 2017 and 2024, reflecting a growing interest in leveraging multimodal neuroimaging techniques to explore AD biomarkers and their impact and influence on functional connectivity (Patel et al., 2020).

Most studies employed a cross-sectional study design (20 studies) rather than a longitudinal (five studies) design, likely due to data availability constraints in having the study resources to run both A β -PET, tau-PET, and resting-state fMRI scans for each participant.

Cross-sectional studies (Schultz et al., 2017; Sepulcre et al., 2017; Zhou & Bai, 2017; Adams et al., 2019; Franzmeier et al., 2019; Lee et al., 2019; Neitzel et al., 2019; Ossenkoppele et al., 2019; Meeker et al., 2020; Quevenco et al., 2020; Schumacher et al., 2021; Liu et al., 2022; Zeng et al., 2022; Cassady et al., 2023; Mijalkov et al., 2023; Millar et al., 2023; Zheng et al., 2023; Abuwarda et al., 2024; Bueichekú et al., 2024; and Canal-Garcia et al., 2024) provide snapshots of how tau and A β impact functional connectivity at specific disease stages, revealing patterns of increased or decreased functional connectivity linked to the accumulation of AD biomarkers.

In contrast, longitudinal studies (Chen et al., 2020; Franzmeier et al., 2020; Köbe et al., 2021; Binette et al., 2022; and Rubinski et al., 2022) offer insight into the progressive nature of tau pathology and its evolving impact on functional connectivity over time. For example, Chen et al. (2020) found that tau spreads from the entorhinal cortex to broader cortical regions over several years, especially when A β is present.

Another study design choice pertained to the chosen populations. Most studies included older adults across multiple AD stages, but the majority of studies within this review included participants without signs of cognitive impairment. This focus suggests an interest in detecting early biomarkers before

clinical symptoms appear, aiming for early intervention in the preclinical stages of AD, which echoes sentiments from Sperling et al. (2011).

We flagged a limitation across several studies that used a comparative sample of young adults. Convenience sampling is common in obtaining samples from this demographic, but its external validity concerns limit it. Recruitment from university or college settings may not represent the broader young population, limiting generalisability (Andrade, 2020). Nevertheless, including younger cohorts can aid in establishing what is a “healthy” baseline for functional connectivity, and doing so may assist in detecting functional connectivity aberrations associated with AD pathology (Negro & Opazo, 2023). Finally, more recent studies, such as Abuwarda et al. (2024) and Bueichekú et al. (2024), utilised large sample sizes (300+ participants). Larger cohorts enhance the findings' statistical power and reliability, enabling more robust conclusions (Columb & Atkinson, 2015). Smaller, more focused cohorts, like those by Cassady et al. (2023) and Zhou & Bai (2017), have smaller sample sizes and are often focused on hypothesis-driven, region-specific analyses.

2.6 Conclusions

This review sought to evaluate and understand the current research landscape of studies employing A β -PET and tau-PET, alongside resting-state fMRI, to measure functional connectivity. Of the 343 records screened, just 25 met our inclusion and exclusion criteria.

Recent research trends suggest a shift towards understanding tau's impact on brain networks. Additionally, most studies included some form of diagnostic group that did not present with evidence of cognitive impairment. We also observed that later studies tended to employ larger sample sizes, presumably for enhanced statistical power and reliability.

This body of research highlights the relationships between functional connectivity and AD pathology. A wide variety of functional connectivity approaches are available, ranging from data-driven approaches to hypothesis-driven approaches. However, studies rarely included both approaches. Therefore, building on these insights may hold promise for early detection, targeted interventions, and the development of personalised therapeutic strategies.

2.7 Aims and Objectives

The primary aim of this project was to deepen our understanding of the relationships between functional connectivity and AD biomarkers - A β and tau - by utilising a broader range of functional connectivity methods. These methods encompassed both “data-driven” and “hypothesis-driven” approaches to build upon existing research.

The objectives of this project were as follows:

- Objective 1: Identify latent functional connectivity patterns across AD groups using whole-brain, data-driven functional connectivity methods.
- Objective 2: To measure whether the regional burden of A β and tau load are associated with functional connectivity patterns identified in Objective 1.
- Objective 3: To determine whether localised A β and tau moderate the relationship between functional connectivity and multidomain cognitive performance.
- Objective 4: Investigate whether functional connectivity within and between the Default Mode network and MTL is associated with regional tau burden (localised to within sub-regions of the Default Mode network and MTL). Furthermore, to evaluate whether A β status (A β + / -) modulates these relationships among a sample of older adults without evidence of cognitive impairment.

2.8 Thesis Structure

Chapter 1: Introduction: Has introduced a broad-level background covering key themes: AD, AD biomarkers, and brain imaging.

Chapter 2: Systematic Literature Review: Described the current AD research linking functional connectivity (measured using resting-state fMRI) and AD biomarkers (measured using both A β -PET and tau-PET).

Chapter 3: Materials and Methods: Describes the two data sources for this project, outlines their study designs and participant characteristics, brain imaging data acquisition protocols (structural MRI, resting-state fMRI, and A β -PET and tau-PET), and data pre-processing, denoising, and quality assessment pipelines.

This section also covers the brain imaging and statistical data analysis methods used for each chapter.

Chapter 4: Differences in Whole-Brain Functional Connectivity Between AD Stages: This chapter covers the first set of analyses comparing whole-brain functional connectivity patterns between AD groups with the inclusion of a sensitive adjustment method to refine a large number of functional connections in a spatially meaningful way.

Chapter 5: Using a Data-Driven Approach to Identify and Extract Key Regions of Functional Connectivity Variability Between AD Stages: Research in this section utilised a supervised machine learning method as an alternative to traditional mass univariate analysis. This approach aimed to extract key brain regions that explain the most variance between AD stages.

Supplementary analyses are then run to explore possible reasons behind non-significant findings between CU and DAT participants by stratifying them into sub-groups based on A β status.

Chapter 6: AD Biomarkers as Moderators of the Relationships Between Functional Connectivity and Multidomain Cognitive Performance: This chapter explores whether AD biomarkers - A β and tau - moderate the relationships between functional connectivity and multidomain cognitive performance.

Chapter 7: Network-Level Functional Connectivity Within and Between the Medial Temporal Lobe and Default Mode Network: Specific Patterns Based on Amyloid Status: This chapter takes an alternative approach with the secondary dataset. Instead of working with whole-brain functional connectivity data, specific areas most closely aligned with tau accumulation are extracted. Functional connectivity is then measured between these regions, and participants are subdivided into A β status groups.

Chapter 8: Overall Discussion and Conclusions: Provides an overall discussion of the main findings of the project, the strengths and limitations, clinical applications, future directions, and conclusions.

Figure 2.2. provides a visual representation of the thesis chapters and their connections to one another.

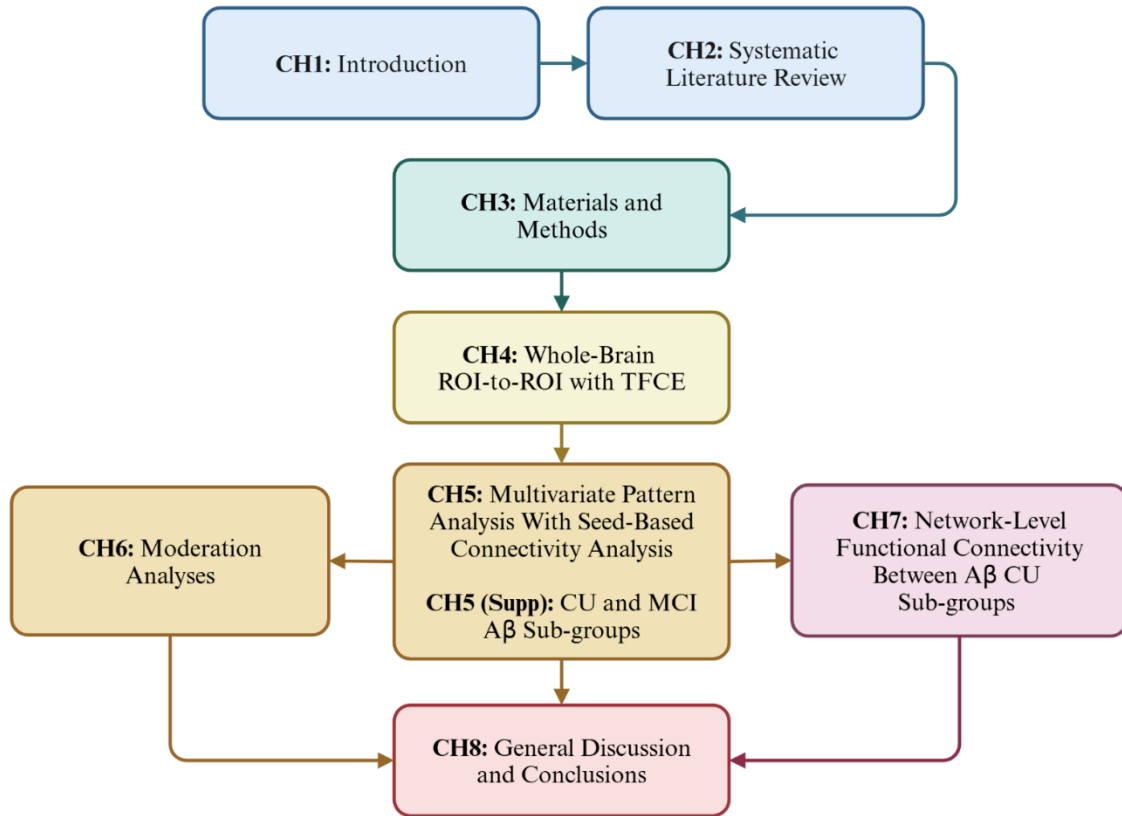


Figure 2.2. Visual representation of thesis chapters.

Note: CH = chapter; ROI = region of interest; TFCE = threshold-free cluster enhancement; CU = cognitively unimpaired; MCI = mild cognitive impairment; A β = amyloid-beta; Supp = supplementary.

Chapter 3: Materials and Methods

3.1 Section A: Methodology

3.1.1 Data Sources

This study utilised two datasets from the ADNI and Open Access Series of Imaging Studies (OASIS) studies. Both datasets were selected for cross-sectional analyses because they included resting-state fMRI, structural MRI, A β -PET, and tau-PET imaging sequences. ADNI data was used for Chapters 4 - 6, and OASIS data was used for Chapter 7.

A comparison of the key similarities and differences between these datasets is presented in Figure 3.1.

The ADNI study began in 2016 and is ongoing (Weiner et al., 2017). At the beginning of this project in October 2020, we opted to use data derived from (at the time) the latest phase. The primary goal of ADNI-3 is to explore the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics across the entire spectrum of Alzheimer’s disease (*“About ADNI”*, n, d). A notable advancement in ADNI-3 compared to earlier phases is the exclusive use of 3 Tesla MRI scanners, which were implemented to establish a standardised imaging protocol (Weber et al., 2021). ADNI is now in its fourth phase, with study enrolment beginning in 2023 (*“ADNI 4”*, n, d)

The OASIS study aims to provide open access to multimodal imaging datasets (LaMontagne et al., 2019), with the most recent releases being OASIS-3 and OASIS-4². For this project, data was obtained from the OASIS-3 Tau (*“OASIS-3_AV1451”*) cohort through the XNAT Central portal³. The tau-PET scan date for OASIS-3_AV1451 participants was used as a reference to select the nearest T1-structural MRI, resting-state fMRI, and A β -PET scans within a six-month timeframe: “to the best effort of investigators, participants underwent scan sessions within six months of Clinical Core visits” (LaMontagne et al., 2019).

² <https://sites.wustl.edu/oasisbrains/>

³ <https://sites.wustl.edu/oasisbrains/central-xnat/>

3.1.2 Study Participants

For data derived from ADNI-3, newly enrolled older adults aged 60 - to - 90 years (inclusive) were used for cross-sectional analyses. We included 252 participants across the AD spectrum: those who ADNI described as cognitively normal (CN; hereby referred to as cognitively unimpaired [CU]; [$n = 167$]), had amnesic-mild cognitive impairment (MCI; denoted hereafter as MCI; $n = 68$), or mild-AD (hereby referred to as dementia of the Alzheimer's type [DAT]; $n = 17$). The rationale for changing these diagnostic labels is covered in section 3.1.2.1.

In ADNI-3, a research diagnosis of CU, MCI, or DAT was based on the following neuropsychological test criteria:

- CU eligibility criteria: Clinical Dementia Rating (CDR; Morris, 1993) memory box score = 0; Mini-Mental State Exam (MMSE; Folstein et al., 1975; Kurlowicz & Wallace, 1999) = 24 – to - 30; and Logical Memory II subscale (derived from the Wechsler Memory Scale-Revised [Wechsler, 1987]) ≥ 9 for those with 16+ years of education, ≥ 5 for 8 – to - 15 years of education, and ≥ 3 for 0 – to - 7 years of education.
- MCI eligibility criteria: CDR memory box score = .5; MMSE 24 – to - 30; Logical Memory II subscale ≤ 11 for 16+ years of education, ≤ 9 for 8 – to - 15 years of education, ≤ 6 for 0 – to - 7 years of education.
- DAT eligibility criteria: Subjective memory concern disclosed by the participant, study partner, or a clinician; CDR memory box score = .5 or 1; MMSE = 20 – to - 26; Logical Memory II subscale ≤ 8 for 16+ years of education, ≤ 4 for 8 – to - 5 years of education, ≤ 2 for 0 – to - 7 years of education.

Other eligibility inclusion and exclusion factors are covered in Appendices 1.1 and 1.2.

Cross-sectional analyses using OASIS-3 study included participants based on three sets of criteria: (1) individuals who were determined as “generally healthy” (by the OASIS team), were CN (similarly with ADNI-3, CN participants will now be referred to as CU), had a CDR score of 0, had a family history of AD; (2) individuals who were “generally healthy”, were CU (CDR = 0), and had no family

history of AD; and (3) healthy individuals 65+ years, both those who were CU (CDR = 0) and those with “very mild symptomatic AD” (CDR = .5 and 1; LaMontagne et al., 2019). For this thesis, only participants defined as CU were included for analysis using OASIS-3 data ($n = 287$).

Like with ADNI-3, further eligibility inclusion and exclusion factors are covered in Appendix 1.3.

3.1.2.1 Research Diagnostic Labels

This thesis used three diagnostic group labels: CU, MCI, and DAT. Both ADNI-3 and OASIS-3 used the label “CN” to refer to participants with no evidence of cognitive impairment. ADNI-3 also used “AD” to designate individuals with Alzheimer's disease. For this thesis, we chose to use “CU” instead of “CN” to avoid implying a baseline of normalcy, which can be subjective (a sentiment echoed based on the outcomes of a scoping review by Sims et al., 2021). “CU” better reflects participants who have no cognitive impairment but may still present elevated AD biomarkers, as seen in Chapters 5 and 7.

We used “DAT” in place of “AD” because, in the ADNI-3 study, participants were assigned a research diagnosis of AD based on neuropsychological test scores, not on the presence of biomarkers such as A β and tau (see also a review by Jalbert et al., 2008). These individuals showed significant cognitive deficits at screening per the aforementioned screening criteria. Despite this, we found that all 17 ADNI-3 participants included in this thesis with a research diagnosis of AD also had evidence of elevated cortical A β levels (via A β -PET).

The label “MCI” used in ADNI-3 was not changed for this thesis.

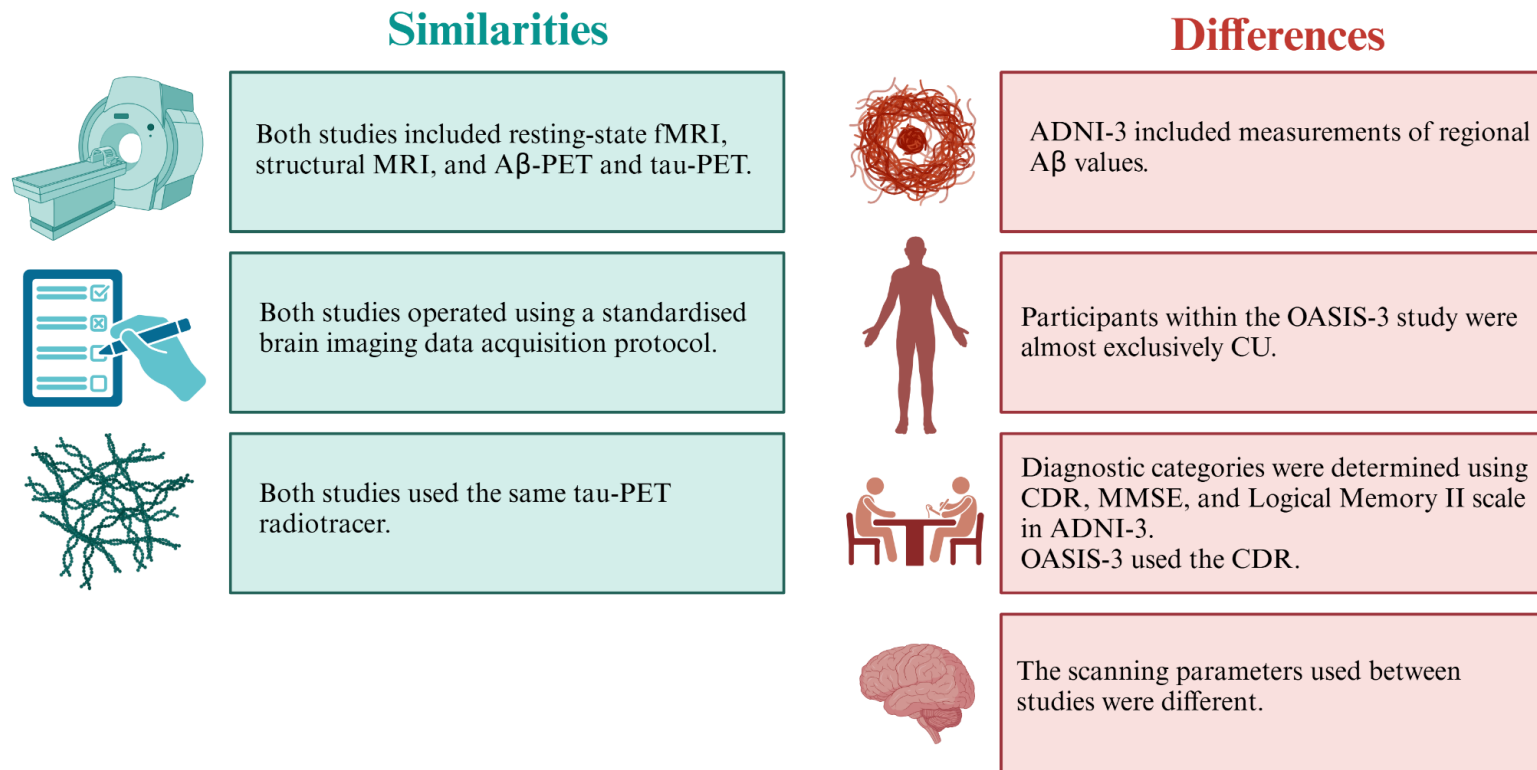


Figure 3.1. Similarities and differences between the ADNI-3 and OASIS-3 studies.

Note: ADNI-3 = Alzheimer’s Disease Neuroimaging Initiative – phase three cohort; OASIS-3 = Open Access Series of Imaging Studies – phase three cohort; (f)MRI = (functional) magnetic resonance imaging; PET = positron emission tomography; A β = amyloid-beta; CU = cognitively unimpaired; CDR = Clinical Dementia Rating; MMSE = Mini Mental-State Examination. Created with BioRender.com.

3.1.3 Materials and Instruments

3.1.3.1 Brain Imaging

3.1.3.1.1 Brain Imaging Software

The Neuroimaging Tools and Resources Collaboratory⁴ was used to download all relevant brain imaging software (except Horos).

Horos (version 3.3.2; 2024)⁵ was downloaded to store .dcm files and to visually inspect structural and functional brain slices (see Figure 3.2.). MRICrogl (Rorden & Brett, 2000) was used to convert .dcm files to .nii format. Next, the CONN toolbox (Version 21a; Whitfield-Gabrieli & Nieto-Castanon, 2012) was run in MATLAB (version R2022a, MathWorks Inc., 2022) for data pre-processing, denoising, quality checking, and analysis. This software uses scripts from Statistical Parametric Mapping 12 (SPM12; Friston, 2003).

The “Functional Magnetic Resonance Imaging of the Brain Software Library” (FSL; version 6.0.7.13; Smith et al., 2004) allowed for the construction of custom brain imaging masks, which are not available in CONN (see section 3.1.3.1.4). Freeview (in FSL) was used to view these custom brain masks and to access the Desikan template (Desikan et al., 2006).

MRICrogl was also used to identify areas of brain activation with the AAL atlas (Rolls et al., 2020) overlaid onto a standardised structural magnetic resonance image.

3.1.3.1.2 MRI Data Acquisition

Participants’ MRI and resting-state fMRI data at baseline were downloaded from the ADNI Laboratory of Neuroimaging website⁶. Three-dimensional T1-weighted Magnetisation Prepared Rapid Gradient Echo MRI scan sessions were conducted using 3 Tesla scanning hardware. For Magnetisation Prepared Rapid Gradient Echo scans, the protocol was as follows: field of view = 208 x 240 x 256mm³ at 1 x 1 x 1mm³ resolution; TE = minimum full echo; TR = 2300ms; 2x accelerated image acquisition sequence; and a scanning time = ~6:20mins. For Echo Planar Imaging-BOLD task-free resting-state

⁴ <https://www.nitrc.org/>

⁵ <https://horosproject.org/>

⁶ <https://ida.loni.usc.edu/login.jsp?project=ADNI>

fMRI scans: voxel size = $3.39 \times 3.39 \times 3.39\text{mm}^3$; TE = 56ms; TR = 3000 ms; 2x accelerated image acquisition sequence; and a scanning time = ~10mins. Image acquisition was performed at multiple sites using a standardised MRI protocol (see Weber et al., 2021 for further details).

The structural MRI data in the OASIS-3 study were acquired using 3 Tesla Siemens scanners with T₁-weighted Magnetisation Prepared Rapid Gradient Echo sequences. Key parameters include a repetition time of approximately 2400ms, an echo time of around 2.20 to 3.16ms, and an inversion time of 1000ms. The flip angle ranged between 8 to 10 degrees, with a voxel size of 1mm^3 isotropic. The field of view was set at 256 mm, and the matrix size was 256 x 256.

The OASIS-3 study utilised Echo Planar Imaging sequences on 3 Tesla Siemens scanners for the resting-state fMRI data. The TR for these scans was 2.20 seconds, with an echo time of 27 ms and a flip angle of 90 degrees. The voxel size was set at 4mm^3 isotropic, and the field of view was 256mm with a matrix size of 64 x 64. Participants were asked to lie quietly with their eyes open while two 6-minute resting state BOLD sequences were collected to evaluate neural activity at rest (LaMontagne et al., 2019).

The ADNI-3 and OASIS-3 datasets were not merged due to variations in MRI and fMRI data acquisition methods, including differences in scanner hardware, voxel sizes, and acquisition parameters. As such, these variations can introduce systematic biases (Poline et al., 2012).

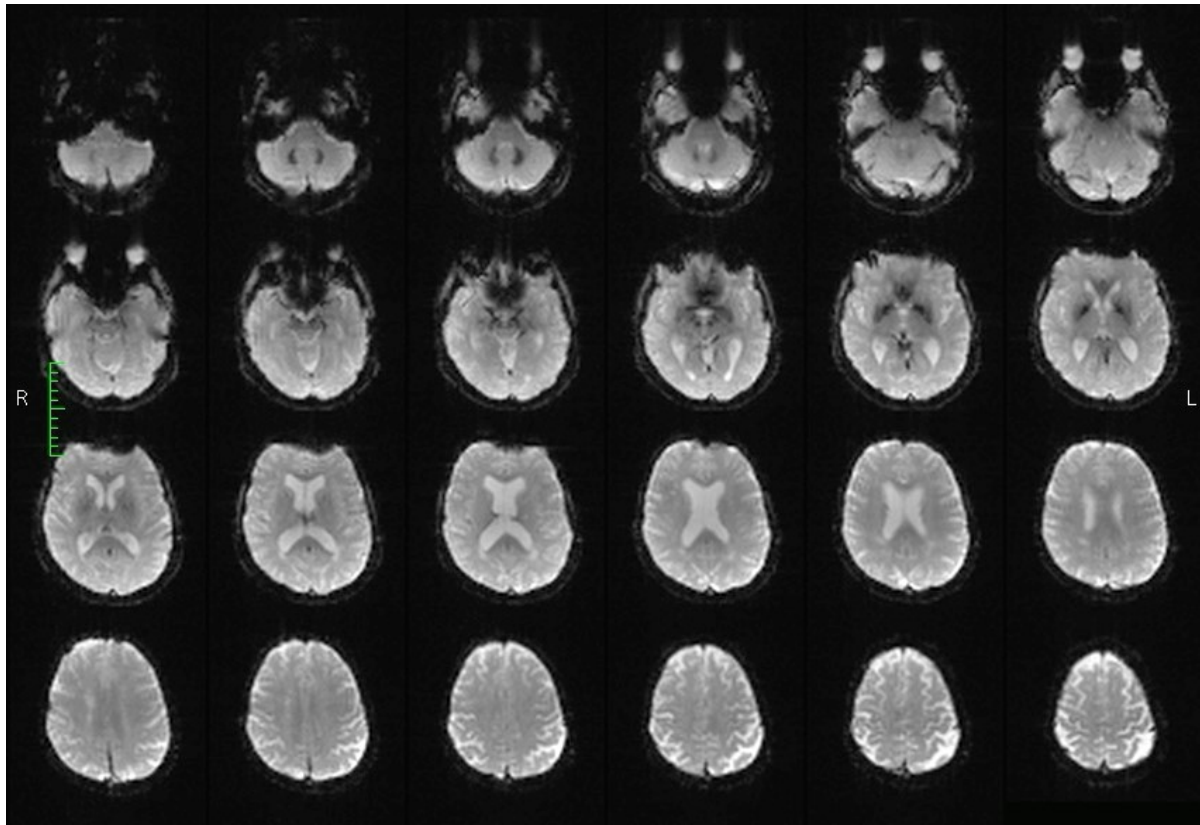


Figure 3.2. Example of resting-state fMRI brain slices for a single participant

Note: The image was produced using Horos. Uncompressed axial slices of a single participant are used to exemplify the use of this software for data visualisation. R = right; L = left.

3.1.3.1.3 MRI Preprocessing, Denoising, and Quality Control

The same pre-processing and denoising pipelines were used for ADNI-3 and OASIS-3 data. Structural MRI and fMRI data were pre-processed using the CONN toolbox (version 21a; Whitfield-Gabrieli & Nieto-Castanon, 2012). CONN's default preprocessing pipeline was chosen. First, resting-state fMRI data was realigned using SPM12's realign and unwarping procedure (see Andersson et al., 2001). Magnetisation-prepared Rapid Gradient Echo and resting-state fMRI scans were then co-registered and resampled for the first scan using *b*-spline interpolation. Next, slice time correction for temporal misalignments was made due to images being acquired in two-dimensional slices over time, whereby fMRI data is time-shifted and resampled using *sinc*-interpolation to match the time in the middle of each TA (acquisition time). Then, due to resting-state's increased susceptibility to motion artefacts, CONN's outlier detection step identifies outlier scans from the observed global BOLD signal, providing detailed estimates of the amount of participant motion using Artifact Detection Tool-based scrubbing. This study considered scans with framewise displacement >.9 millimetre or global BOLD signal changes above five standard deviations as evidence of excessive motion. Functional and structural volumes were segmented into separate tissue classes and normalised into standard Montreal Neurological Institute (MNI) space (Mazziotta et al., 1995). Resting-state fMRI data were then smoothed using spatial convolution with a Gaussian kernel of 8mm full-width half-maximum to increase BOLD signal-to-noise. Furthermore, due to resting-state's susceptibility to motion and physiological-based artifacts, CONN also utilises a denoising pipeline that broadly includes two focus areas: (1) linear regression of potential confounding effects in the BOLD signal (e.g., "anatomical Component-based noise Correction" tool [Behzadi et al., 2007]), and (2) temporal band-pass filtering (.008 hertz or above .09 hertz).

Quality control was undergone at all levels, beginning at the raw level, in which visual inspection of each participant's imaging data was conducted using multislice interactive displays. Next, quality control of the imaging data at the pre-processing and denoising levels was guided by visual quality checks of plots and inspecting CONN's automated quality control summary outputs (Morfini et al., 2023).

3.1.3.1.4 PET Data Acquisition

For this thesis, participants who had received both an A β -PET and tau-PET scan were selected. For amyloid imaging, ADNI-3 used one of two radiotracers: ^{18}F -Florbetaben or ^{18}F -Florbetapir, and one tau radiotracer - ^{18}F -AV-1451 (Flortaucipir / AV1451). All participants had a 20-minute continuous brain PET scan beginning at either 50 minutes (^{18}F -Florbetapir) or 90 minutes (^{18}F -Florbetaben). For ^{18}F -AV-1451, a 30-minute dynamic scan was acquired approximately 75 minutes post-injection. For more information, see Lee et al. (2023).

Next, for analyses using OASIS-3 data, all participants receiving a tau-PET had the ^{18}F -AV-1451 radiotracer (as with ADNI-3). Participants received an A β -PET using one of two radiotracers: ^{18}F -Florbetapir or ^{11}C -Pittsburgh compound B for global A β burden. All PET imaging analyses are performed using the PET unified pipeline (Su et al., 2013; 2015). Further details regarding the PET data acquisition parameters can be found in LaMontagne et al. (2019).

In the “OASIS-3_AV1451” sub-cohort of OASIS-3, participants also underwent ^{18}F -AV-1451 tau-PET scans, allowing for the assessment of regional tau burden within specific brain regions corresponding to Braak stages 1 to 6 (Braak & Braak, 1991). The brain regions associated with each Braak stage are as follows:

- Braak stages 1 and 2: Entorhinal cortex,
- Braak stages 3 and 4: Amygdala, Accumbens area, hippocampus, insula, medial orbitofrontal gyrus, lateral orbitofrontal gyrus, pars orbitalis, parahippocampal cortex, rostral anterior cingulate cortex, posterior cingulate cortex, caudal anterior cingulate cortex, and isthmus cingulate cortex, and
- Braak stages 5 and 6: Banks of the superior temporal sulcus, middle temporal gyrus, caudal middle frontal gyrus, fusiform gyrus, inferior parietal gyrus, inferior temporal gyrus, lateral occipital gyrus, supramarginal gyrus, and precuneus.

For corresponding Freesurfer labels of these brain regions, see Table 3.1.

Table 3.1. Brain regions corresponding to each Braak stage and their respective Freesurfer labels

Braak Stages	Freesurfer Region Processing Name	Brain Region
<i>1 and 2</i>	ctx-entorhinal	Entorhinal cortex
<i>3 and 4</i>	Amygdala	Amygdala
	Accumbens-area	Accumbens area
	Hippocampus	Hippocampus
	ctx-insula	Insula
	ctx-medialorbitofrontal	Medial orbitofrontal cortex
	ctx-lateralorbitofrontal	Lateral orbitofrontal cortex
	ctx-parsorbitalis	Pars orbitalis
	ctx-parahippocampal	Parahippocampal cortex
	ctx-rostralanteriorcingulate	Rostral anterior cingulate cortex
	ctx-posteriorcingulate	Posterior cingulate cortex
	ctx-caudalanteriorcingulate	Causal anterior cingulate cortex
	ctx-isthmuscingulate	Isthmus cingulate
	ctx-bankssts	Banks of the temporal sulcus
	ctx-middletemporal	Middle temporal gyrus
<i>5 and 6</i>	ctx-caudalmiddlefrontal	Caudal middle frontal gyrus
	ctx-fusiform	Fusiform gyrus
	ctx-inferiorparietal	Inferior parietal gyrus

ctx-inferiortemporal	Inferior temporal gyrus
ctx-lateraloccipital	Lateral occipital gyrus
ctx-supramarginal	Supramarginal gyrus
ctx-precuneus	Precuneus

Notes. ctx=cortex.

3.1.3.1.4.1 SUVr and Centiloid

SUVr and Centiloid are both metrics used in PET imaging to quantify the amount of radiotracer uptake, e.g., A β and tau:

1. SUVr is a semi-quantitative measure used in PET imaging to assess the relative concentration of a radiotracer in a target brain region compared to a reference region (Joshi et al., 2012). SUVr is calculated by dividing the average uptake of the radiotracer in an ROI by the average uptake in a reference region (Joshi et al., 2012). This region is assumed to be relatively unaffected by the target (e.g., the cerebellum is used widely in AD studies measuring A β accumulation via A β -PET (Joshi et al., 2012). It is calculated using the following formula:

$$SUVr = \frac{SUV_{Target\ Region}}{SUV_{Reference\ Region}}$$

Equation 3.1. The calculation for SUVr

Note: Where $SUV_{Target\ Region}$ = the standardised uptake value within the region of interest and $SUV_{Reference\ Region}$ = the standardised uptake value within the reference region (e.g., the cerebellum).

2. The centiloid scale is a standardised system used to quantify amyloid deposition in the brain, primarily in AD research and clinical settings (Klunk et al., 2014). The scale ranges from 0 to

100, with 0 representing no amyloid and 100 indicating the maximum amyloid burden observed in advanced AD. The scale is derived by calculating the SUV_R , which normalises amyloid uptake in the brain's target regions to a reference region. SUV_R values are then linearly transformed to the centiloid scale using a formula specific to each PET tracer, aligning them with the Pittsburgh Compound B PET “gold standard”. The centiloid scale allows for consistent comparison of amyloid between studies (Klunk et al., 2014).

3.1.3.1.4.2 A β -PET Status Thresholds and Tau-PET Braak Staging

The University of California, Berkeley, established cut-off thresholds for A β status (+ / -) using A β -PET with one of two radiotracers: either Pittsburgh compound B or ^{18}F -AV-45 (florbetapir / AV45). A β status was determined based on two A β centiloid cut-offs: 16.40 for Pittsburgh compound B and 20.60 for AV45.

ADNI-3 data were normalised with whole cerebellum reference region thresholds for two A β -PET radiotracers: ^{18}F -Florbetaben and ^{18}F -Florbetapir. The SUV_r values for A β + cut-offs were ≥ 1.08 for ^{18}F -Florbetaben and ≥ 1.11 for ^{18}F -Florbetapir. This was in line with the recommendations of Lee et al. (2023) and Joshi et al. (2012).

Additionally, for Chapter 7, participants were measured in accordance with their Braak staging (and measured using ^{18}F -AV-1451 PET). This was in line with research by Chen et al. (2021), whereby participants were assigned to stages based on the severity of tau accumulation within Braak stages 1 to 6 using the following criteria: participants with Braak 5 / 6 ROI $SUV_r > 1.873$ were assigned as severity stage 4; participants with Braak 3 / 4 ROI $SUV_r > 1.523$ were classified as severity stage 3; participants with Braak 3 / 4 ROI $SUV_r > 1.307$ fell into severity stage 2; participants with Braak 1 / 2 ROI $SUV_r > 1.129$ as severity stage 1; and lastly, participants with Braak 1 / 2 ROI $SUV_r \leq 1.12$ were assigned severity stage 0.

3.1.3.2 Neuropsychological Testing

3.1.3.2.1 NEUROBAT

For measures of neuropsychological testing with ADNI-3 participants' data, sub-tasks of the Neuropsychological Battery (also referred to as "NEUROBAT") were used to extract data pertaining to different cognitive domains (see Table 3.2.). NEUROBAT data was downloaded from the ADNI Laboratory of Imaging website and cleaned to include relevant neuropsychological variables. Sub-tasks of the NEUROBAT and which cognitive sub-domain they measure are as follows:

- **Episodic Memory (Immediate and Delayed):** The Rey Auditory Verbal Learning Test assesses verbal learning and memory (Bean, 2011). This test comprises a series of list-learning exercises to recall as many words from a list of 15 nouns as possible. The free recall test component spans over five repetitions, including an interference list (List B). Delayed memory is measured after a 20-minute delay, and the participant is asked to recall the words from List A again (a measure of delayed recall). Next, recognition memory is measured by presenting the participant with 50 words containing all the words from Lists A (free recall) and List B (interference), in addition to 20 phonemically and semantically similar words (Bean, 2011). Total free recall and delayed recall will be added as immediate and delayed memory measures, respectively.
- **Visuospatial Processing: Clock Drawing (Command and Copy conditions).** In the command condition, the participant is asked to complete three instructions: (a) draw the face of a clock, (b) add numbers 1 to 12 in the correct places, and (c) draw the clock hands set for "10 after 11". Afterwards, in the copy condition, participants are asked to copy a clock model (Libon & Penney, 2013). The sum of the copy and command conditions will be used as a total score for Visuospatial processing.
- **Executive Function: The Trail Making Test (parts A and B).** The Trail Making Test was first developed in 1944 (Army Individual Test Battery, 1944). For Part A, the participant uses a pencil to connect the circles sequentially numbered 1 to 25. Part A is a measure of psychomotor processing speed. Part B involves linking a number and letter (e.g., 1 to A; A to 2; 2 to B, etc.). Unlike Part A, this task is considered a measure of executive function, specifically, set

switching and divided attention. Therefore, only Part B was included in further statistical analyses to measure executive function.

- Language: Category Fluency Test (Animals) and the Multilingual Naming Test. The Category Fluency Test information was derived from the “*ADNI-3 Procedures Manual*” (2017)⁶. Specifically for the Animals category, participants are given the following instructions:

“Now, I want you to name things that belong to another category: Animals. You will have one minute. I want you to tell me all the animals you can think of in one minute” “*ADNI-3 Procedures Manual*” (2017)⁷.

The number of actual responses is recorded. Correct, unique animal names are scored positively. Intrusions are defined as any word that does not fit the Animals category, and perseverations are repetitions of any animal already verbally spoken. The sum of the Category Fluency Test and Multilingual Naming Test will be used as a total score for Language.

3.1.3.2.2 CDR

Washington University’s CDR (Morris, 1993) was used to facilitate a research diagnosis for participants within the ADNI-3 and OASIS-3 studies. The CDR is a semi-structured interview five-point scale used to determine whether the participant has signs of dementia and is scored on a scale between 0 (no impairment), .5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia) that is characterised by scoring six domains (memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care).

3.1.3.2.3 MMSE

The MMSE was used in the ADNI-3 study to supplement the information of the CDR and Logical Memory II subscale (derived from the Wechsler Memory Scale-Revised; Wechsler, 1987). It is a 30-question cognitive screening tool that measures evidence of cognitive impairment, assessing cognitive

⁷ <https://adni.loni.usc.edu/adni-3/procedures-manuals/>

facets such as orientation, recall, language, attention, and calculation, among other aspects (Folstein et al., 1975; Kurlowicz & Wallace, 1999).

3.1.3.2.3 Logical Memory II Subscale (Wechsler Memory Scale-Revised)

The Logical Memory II test is one component of the Wechsler Memory Scale (Wechsler, 1987). The Logical Memory subtest specifically assesses verbal memory, with Logical Memory II focusing on delayed recall. In short:

- Logical Memory I (Immediate Recall): Participants are read two short passages and are asked to recall as many details as possible immediately after each passage is read (Wechsler, 1987).
- Logical Memory II (Delayed Recall): After a delay (of approximately 20 to 30 minutes), participants are asked to recall the details of the passages they heard earlier (without prompts; Wechsler, 1987).

Table 3.2. NEUROBAT cognitive domains

Domain	Notes	ADNI Code
<i>Episodic Memory</i>		
<i>Immediate</i>	The sum of five trials	RAVLT_immediate
<i>Delayed</i>	30-minute delay total	AVDEL30MIN
<i>Visuospatial Processing</i>	The summed score of the clock drawing test (command and copy conditions)	CLOCKSCOR, COPYSCOR
<i>Executive Function</i>	Trail Making Test – Part B trial used (as Part A measured psychomotor speed [and not executive function])	TRABSCOR
<i>Language</i>	The summed score of Categories (Animals) and Multilingual Naming Test	CATANIMSC, MINTTOTAL

Notes: ADNI = Alzheimer’s Disease Neuroimaging Initiative; RAVLT_immediate = Rey Auditory Verbal Learning_immediate; AVDEL30min = auditory verbal delay 30-minutes; CLOCKSCOR = Clock Drawing Test: command condition; COPYSCOR = Clock Drawing Test: copy condition; TRABSCOR = Trail Making Test Part B score; CATANIMSC = Category Fluency Test animals condition; MINTTOTAL = Multilingual Naming Test total score.

3.2 Section B: Data Analysis

3.2.1 Brain Imaging Analysis Methods

Brain imaging analyses were conducted under two broad “themes” (also see Figure 3.3. and Table 3.3.):

1. “Data-driven” approaches, and
2. “Theory-driven” approaches.

For all analyses, age, sex, and total brain volume were controlled for as covariates of no interest.

Data-Driven vs. Hypothesis-Driven Approaches

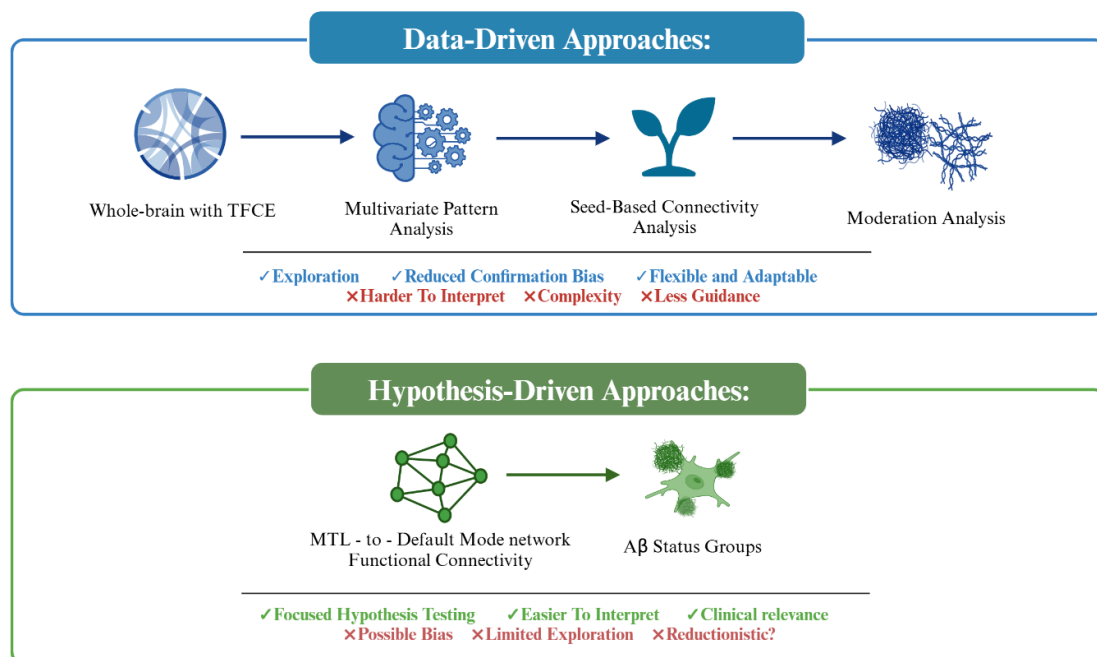


Figure 3.3. Illustration depicting the differences between data-driven and hypothesis-driven functional connectivity approaches

Note: TFCE = threshold-free cluster enhancement; MTL = medial temporal lobe; Aβ = amyloid-beta.

The arrows used in this figure represent the order in which each approach was used.

Created with BioRender.com.

Table 3.3. Summary of functional connectivity and statistical analysis methods used in this project

Results Chapter	Functional Connectivity Method	Data-driven or Hypothesis-driven Approach?	Inferential Statistics Approach
<i>Chapter 4</i>	Whole-brain ROI-to-ROI with TFCE	Data-driven	–
	Graph Theory		
	Multivariate Pattern Analysis		
<i>Chapter 5</i>	Seed-Based Connectivity Analysis	Data-driven	–
	Graph Theory		
	Multivariate Pattern Analysis		
<i>Chapter 5 (Supplementary)</i>	Whole-brain ROI-to-ROI with TFCE	Data-driven	–
	Multivariate Pattern Analysis		
	Network-level ROI-to-ROI		
	Graph Theory		
<i>Chapter 6</i>	–	–	Simple Moderation Analysis
<i>Chapter 7</i>	Network-level ROI-to-ROI	Hypothesis-driven	Spearman's Rank
			PCA
			Robust Linear Regression

Notes. ROI = region of interest; TFCE = threshold-free cluster enhancement; PCA = principal components analysis.

3.2.1.1 Whole-Brain ROI-to-ROI Analysis

In Chapter 4, ROI-to-ROI functional connectivity was calculated between each ROI across the whole brain (164 ROIs [the maximum number of ROIs in CONN]), forming a 164 x 164 statistical matrix denoting 26,896 functional connections for all 252 participants. This was conducted to explore and identify ROI-to-ROI connections demonstrating significant differences between disease categories (CU, MCI, and DAT). The main effect differences between disease stages were explored - CU vs. MCI, CU vs. DAT, and MCI vs. DAT.

Later, supplementary analyses were conducted in Chapter 5 to explore differences in functional connectivity patterns between CU and MCI A β ⁺ / -. Therefore, main effect differences were analysed between CU A β ⁻, CU A β ⁺, MCI A β ⁻, and MCI A β ⁺. Specifically comparing functional connectivity “within” and “between” these two diagnostic categories: (1) CU A β ⁻ vs CU A β ⁺; (2) MCI A β ⁻ vs MCI A β ⁺; (3) CU A β ⁻ vs MCI A β ⁻; and (4) CU A β ⁺ vs MCI A β ⁺.

3.2.1.1.1 Threshold Free Cluster Enhancement

Following whole-brain ROI-to-ROI analyses in Chapter 4, cluster-level inferences were made using threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009; Figure 3.4. and Figure 3.5.) to control for type I errors (a false positive, e.g., Banerjee et al., 2009). This study estimated the ROI-to-ROI matrix of t-values using a general linear model and then sorted using optimal leaf ordering for hierarchical clustering (Bar-Joseph et al., 2001). Unlike similar data-reduction methods, such as spatial pairwise clustering, TFCE does not use a pre-defined height threshold (Smith & Nichols, 2009). The TFCE output value is a weighted sum of the entire local clustered signal without a pre-defined threshold. The TFCE image can be turned into voxel-wise *p*-values for inference via permutation testing (Smith & Nichols, 2009). Therefore, TFCE improves sensitivity to other methods (e.g., spatial pairwise

clustering; Smith & Nichols, 2009). In the current study, the expected distribution of TCFE values under the null hypothesis is numerically estimated (1,000 permutations of the original data) for each cluster with a peak-level FDR-corrected p -value set at $< .05$. The main effect differences between disease stages were explored: CU vs. MCI, CU vs. DAT, and MCI vs. DAT.

When applying TFCE to neuroimaging data, the output is a TFCE-enhanced statistical map where the statistical significance of brain activity is not only more pronounced but also spatially extended. By doing so, TFCE highlights regions that are not only statistically significant but also have a more spatially coherent signal, reducing the impact of noise and isolated voxel activations. Once the TFCE-enhanced map is generated, a significance threshold is applied to identify clusters of activity that surpass a predefined statistical criterion (e.g., p -value $< .05$, corrected for multiple comparisons). These significant clusters, identified through thresholding, are then extracted as ROIs. In this thesis, ROIs were also defined based on their peak activation coordinates.

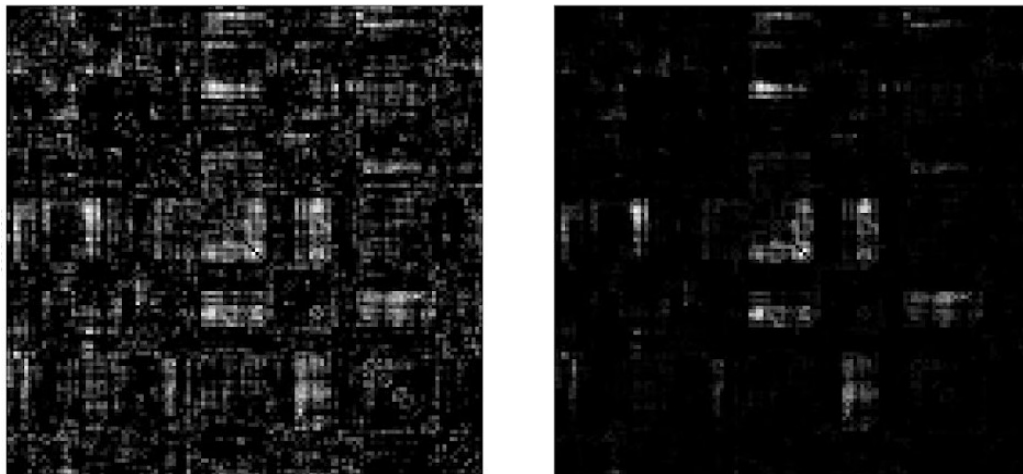


Figure 3.4. The application of Threshold-Free Cluster Enhancement (TFCE) using the CONN toolbox for functional connectivity analysis. The left panel shows the original connectivity matrix, where each pixel represents a connectivity value between seed and target regions of interest (ROIs). The right panel displays the same data after TFCE, a method that enhances cluster-like structures without requiring an arbitrary threshold. TFCE increases sensitivity to significant connectivity patterns while reducing noise, highlighting only the most meaningful connections in the network.

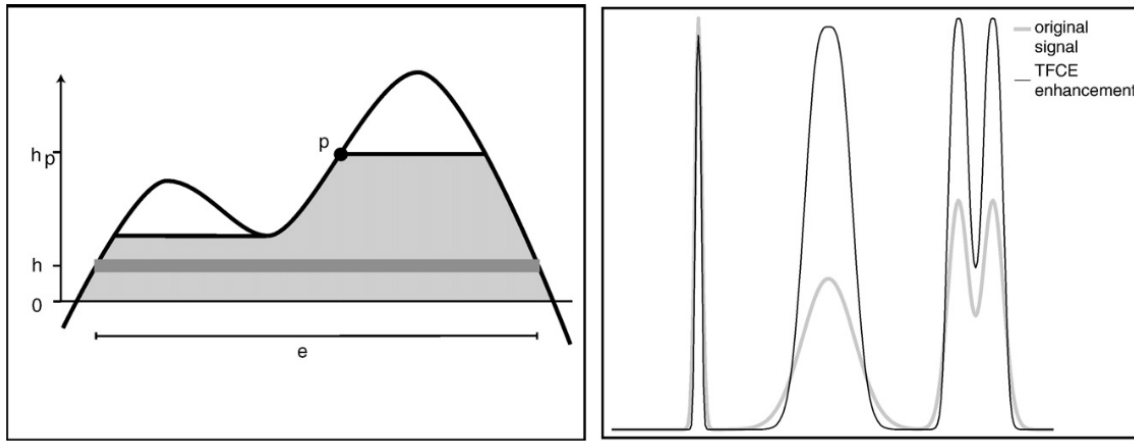


Figure 3.5. Image depicting how TFCE enhances the ability to detect significant brain activity

Note: TFCE = threshold-free cluster enhancement.

Left: The black curve represents a signal/neural activity. A shaded area is shown under the curve between two horizontal lines (labelled as h [lower] and hp [higher]), indicating different thresholds. The horizontal axis (e) represents the extent of the signal, and p represents the peak or specific point of interest (Smith & Nichols, 2009). The TFCE score at a voxel p is calculated by summing the contributions of all incremental signal sections within its support area (Smith & Nichols, 2009). Therefore, the dark grey band represents one such section at a specific intensity level, while the light grey area marks the full extent of connected voxels that contribute to p 's score (Smith & Nichols, 2009).

Right: Two curves are plotted – the “original” and “enhanced” signal (Smith & Nichols, 2009). The black curve represents the “original signal”, and the grey curve represents the “TFCE enhancement” of the signal. The TFCE-enhanced signal shows higher peaks than the original signal, denoting an enhanced ability to detect significant brain activity (Smith & Nichols, 2009).

3.2.1.2 Multivariate Pattern Analysis

In Chapter 5, Multivariate Pattern Analysis allows for measuring network differences at the voxel level (Weaverdyck et al., 2020). CONN computes Multivariate Pattern Analysis functional connectivity maps via PCA. Instead of modelling a seed voxel and analysing each voxel separately, Multivariate Pattern Analysis analyses a set of voxels together, forming a voxel-to-voxel “connectome” (Kazumata et al., 2017).

Multivariate Pattern Analysis extends standard multivariate approaches to examine voxel-wise functional connectivity patterns across subjects (Nieto-Castanon, 2022). Unlike mass-univariate analyses, which assess connectivity for each voxel pair separately, Multivariate Pattern Analysis employs a searchlight approach by analysing functional connectivity patterns between a given seed voxel and the rest of the brain within a multivariate General Linear Model (Nieto-Castanon, 2022). To create a more compact and interpretable representation of functional connectivity patterns, Multivariate Pattern Analysis applies Singular Value Decomposition to extract eigenpatterns - spatial functional connectivity features that maximise intersubject variability (Nieto-Castanon, 2022). These eigenpatterns reduce dimensionality, enabling statistical testing on lower-dimensional representations rather than full functional connectivity matrices (Nieto-Castanon, 2022). The extracted features are then entered into a General Linear Model for hypothesis testing using a Likelihood Ratio Test, generating a brain-wide statistical parametric map that highlights significant functional connectivity differences across conditions or groups (Nieto-Castanon, 2022). Multivariate Pattern Analysis facilitates large-scale analyses without the need to compute full voxel-to-voxel matrices, and this therefore enhances sensitivity in detecting subtle and complex functional connectivity patterns between conditions or groups (Nieto-Castanon, 2022).

Six separate analyses explored the main effect differences between disease stages, e.g., CU vs. MCI, CU vs. DAT, and MCI vs. DAT.

Supplementary analyses were conducted in Chapter 5 to explore differences in functional connectivity patterns between CU and MCI A β + / - (as in Chapter 4).

3.2.1.3 Whole-Brain Seed-Based Connectivity Analysis

Following the Multivariate Pattern Analysis in Chapter 5, whole-brain seed-based connectivity analyses were conducted using ROIs derived from group Multivariate Pattern Analysis. This, therefore, avoids the potential bias often attributed to seed-based connectivity - the *a priori* selection of ROIs (Lv et al., 2018). Group-level differences in seed-to-voxel functional connectivity were determined by disease stage contrasts (as with Multivariate Pattern Analysis, CU vs. MCI, etc.), with functional connectivity strength differences determined by Fisher transformed z-values.

3.2.1.4 ROI-to-ROI: Network-level

To explore the possible reason(s) behind non-significant findings in Chapter 5, further – supplementary – analyses were conducted between CU and MCI participants whilst stratifying these two groups further into A β status sub-groups (CU A β -, CU A β +, MCI A β -, MCI A β +), and comparing functional connectivity “within” and “between” these two diagnostic categories: (1) CU A β - vs CU A β +, (2) MCI A β - vs MCI A β +, (3) CU A β - vs. MCI A β -, and (4) CU A β vs. MCI A β +. Analyses were conducted at the whole-brain levels (as in Chapter 4), using Multivariate Pattern Analysis (as in Chapter 5), and finally at the network level (Table 3.4. and depicted as an image in Figure 3.6.). Network-level analyses were unique to supplementary analyses involving CU and MCI A β status sub-groups due to further non-significant findings at the whole-brain level and when using Multivariate Pattern Analysis (see Chapter 5).

CONN’s eight default resting-state networks were defined using independent components analysis and data derived from the Human Connectome Project ($n = 497$; see “CONN: Functional connectivity toolbox” (2024⁸) and Appendix 1.3.

⁸ <https://github.com/alfnie/conn/blob/master/rois/atlas.descrip.jpg>

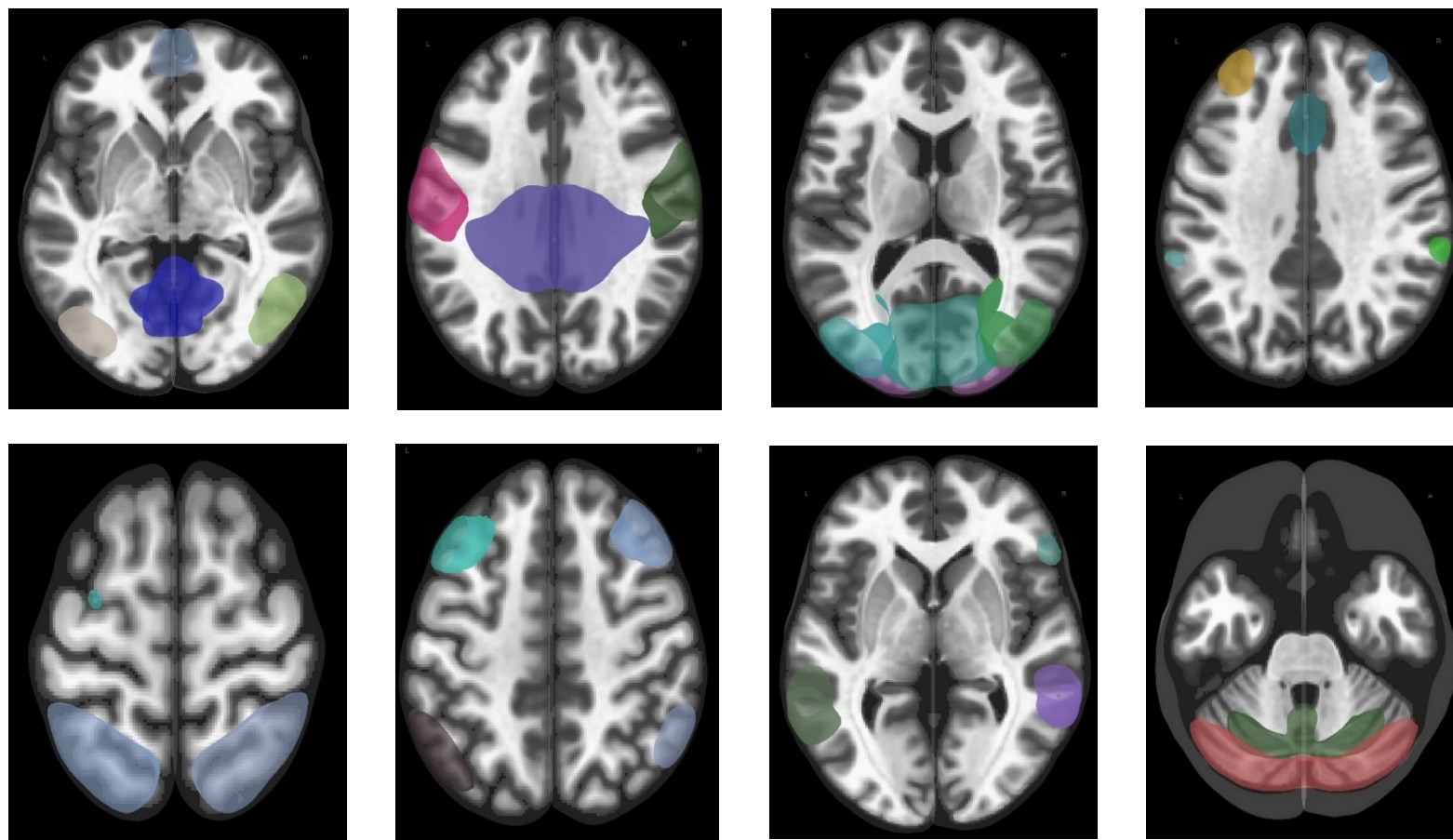


Figure 3.6. Eight resting-state networks

Note: Axial images of resting-state networks. In order (left to right): Default Mode; Sensorimotor; Visual; Salience, Dorsal Attention network; Frontoparietal network; Language network; and Cerebellar network. Image for each brain network produced in the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Table 3.4. Resting-state networks in the CONN toolbox and their sub-regions

Resting-state Network	Sub-regions	CONN Label	MNI Coordinates
			[x y z]
<i>Default Mode</i>	Medial prefrontal cortex	DefaultMode.MPFC	[+01 +55 -03]
	Left lateral parietal cortex	DefaultMode.LP (L)	[-39 -77 +33]
	Right lateral parietal cortex	DefaultMode.LP (R)	[+47 -67 +29]
	Posterior cingulate cortex	DefaultMode.PCC	[+01 -61 +38]
<i>Sensorimotor</i>	Left lateral portion	SensoriMotor.Lateral (L)	[-55 -12 +29]
	Right lateral portion	SensoriMotor.Lateral (R)	[+56 -10 +29]
	Superior portion	Sensorimotor. Superior	[00 -31 +67]
<i>Visual</i>	Medial portion	Visual.Medial	[+02 -79 +12]
	Occipital portion	Visual.Occipital	[00 -93 -04]
	Left lateral portion	Visual.Lateral (L)	[-37 -79 10]
	Right lateral portion	Visual.Lateral (R)	(38,-72,13)
<i>Salience</i>	Anterior cingulate cortex	Salience.ACC	[00 +22 +35]
	Left anterior insula	Salience.AInsula (L)	[-44 +13 +01]
	Right anterior insula	Salience.AInsula (R)	[+47 +14 00]
	Left rostral prefrontal cortex	Salience.RPFC (L)	[-32 +45 +27]
	Right rostral prefrontal cortex	Salience.RPFC (R)	[+32 +46 +27]
	Left supramarginal gyrus	Salience.SMG (L)	[-60 -39 +31]
	Right supramarginal gyrus	Salience.SMG (R)	[+62 -35 +32]
<i>Dorsal Attention</i>	Left frontal eye fields	DorsalAttention.FEF (L)	[-27 -09 +64]
	Right frontal eye fields	DorsalAttention.FEF (R)	[+30 -06 +64]
	Left intraparietal sulcus	DorsalAttention.IPS (L)	[-39 -43 +52]
	Right intraparietal sulcus	DorsalAttention.IPS (R)	[+39 -42 +54]

<i>Frontoparietal</i>	Left lateral prefrontal cortex	FrontoParietal.LPFC (L)	[-43 +33 +28]
	Left posterior parietal cortex	FrontoParietal.PPC (L)	[-46 -58 +49]
	Right lateral prefrontal cortex	FrontoParietal.LPFC (R)	[+41 +38 +30]
	Right posterior parietal cortex	FrontoParietal.PPC (R)	[+52 -52 +45]
<i>Language</i>	Left inferior frontal gyrus	Language.IFG (L)	[-51 +26 +02]
	Right inferior frontal gyrus	Language.IFG (R)	[+54 +28 +01]
	Left poster superior temporal gyrus	Language.pSTG (L)	[-57 -47 +15]
	Right posterior superior temporal gyrus	Language.pSTG (R)	[+59 -42 +13]
<i>Cerebellar</i>	Anterior portion	Cerebellar.Anterior	[00 -63 -30]
	Posterior portion	Cerebellar.Posterior	[00 -79 -32]

Notes. MNI = Montreal Neurological Institute.

Later, in Chapter 7, targeted (or “hypothesis-driven”) analyses were conducted by isolating the MTL and Default Mode networks and measuring functional connectivity within and between these networks, stratifying CU participants into CU A β - and CU A β + sub-categories.

The key sets of regions for Chapter 7 were those forming the MTL and Default Mode network (Figure 3.7.). The MTL encompasses crucial structures like the hippocampus, entorhinal cortex, and parahippocampal cortex, all essential for memory formation, spatial information processing, and navigation, as described in a review by Squire et al. (2004). The Default Mode network, first described by Raichle et al. (2001), includes brain regions such as the medial prefrontal cortex, posterior cingulate cortex, precuneus, and inferior parietal lobule (Raichle et al., 2001). These regions demonstrate synchronised activity during rest and introspective processes such as self-referential thinking, daydreaming, mind wandering, and recalling personal experiences (Raichle et al., 2001; Greicius et al., 2003; Huntley et al., 2021).

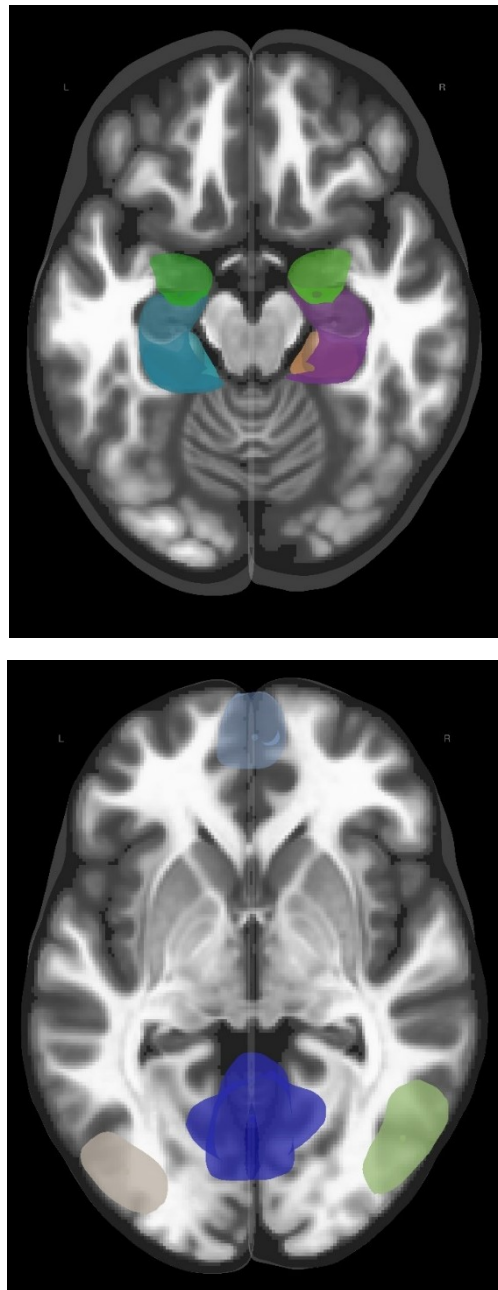


Figure 3.7. The MTL and default mode network

Note: *Top*: Axial display of the medial temporal lobe (MTL), created in the CONN toolbox. The MTL comprised the left and right portions of the hippocampus, left and right parahippocampal gyri (both anterior and posterior subdivisions), left and right amygdala, and left and right entorhinal cortices.

Bottom: Axial display of the Default Mode network. The Default Mode network comprised the medial prefrontal cortex, posterior cingulate cortex, and left and right lateral parietal cortex.

Image for each brain network produced in the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012).

The CONN toolbox does not have a region mask for the entorhinal cortex. Therefore, Freesurfer (version 7.4.1) was used to parcellate the brain and create anatomical masks for this project using the Desikan-Killiany atlas (Desikan et al., 2006; specifically, the “aparc.DKTatlas+aseg.mgz” file and a T1 structural image standardised in MNI space for reference). The left and right portions of the entorhinal cortex were isolated as separate ROIs using reference labels derived from the FreeSurferColorLUT.txt file (label value 1006 for the left entorhinal cortex and 2006 for the right entorhinal cortex; see Figure 3.8.) and visualised in FreeView. Both .mgz files were imported into the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The ROIs were then integrated into the Setup space within the graphic user interface and denoised (e.g., linear regressions of potentially confounding effects; Figure 3.9.).

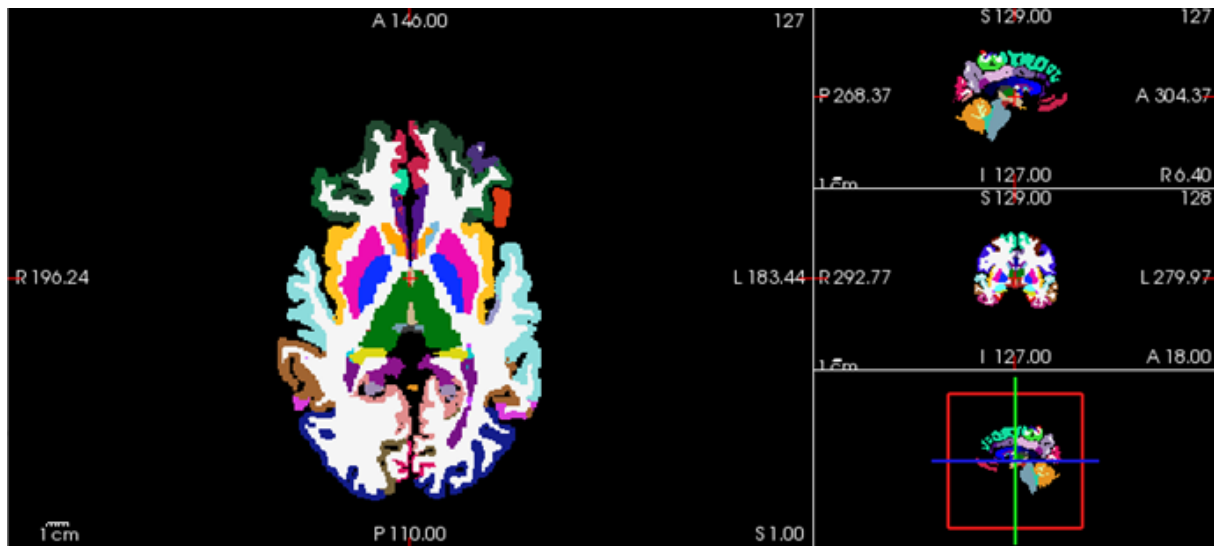


Figure 3.8. Freeview graphic user interface with a T1-structural magnetic resonance image parcellated using the Desikan-Killiany atlas

Note: Desikan-Killiany atlas (Desikan et al., 2006).

Left: axial view.

Right: top = sagittal view; middle = coronal view; bottom = sagittal view with cross-reference lines.

Colours indicate different brain regions.

R = right; L = left; A = anterior; P = posterior.

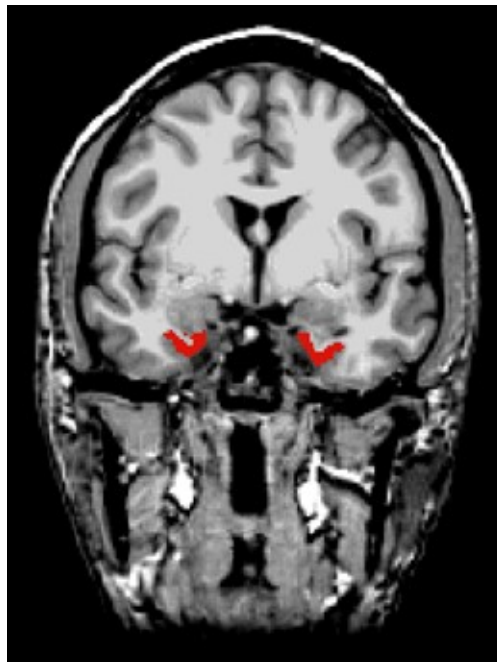


Figure 3.9. The entorhinal cortex's left and right portions depicted on a high-resolution T1 structural image.

Note: Regions of interest were created in Freesurfer and uploaded to the CONN toolbox to be included as sub-regions of the medial temporal lobe. Shown in red.

Once the left and right entorhinal cortex masks were created, functional connectivity was calculated within and between the MTL and Default Mode network. MTL comprised the left and right hippocampus, left and right parahippocampal cortex (anterior and posterior subdivisions), left and right amygdala, and left and right entorhinal cortex (10 total regions). The Default Mode network was defined via the medial prefrontal cortex, posterior cingulate cortex, and left and right lateral parietal cortex (four regions total). Between 14 regions, this resulted in a total of 182 connections (minus self-connections). Age, sex, and an adjusted total brain volume (TBV) value were used as covariates of no interest. The adjusted TBV was calculated as $TBV \sim \text{intracranial volume (ICV)}$ (linear regression model to compute slope β with the formula: dependent variable $\sim$ independent variable; in accordance with Voevodskaya et al., 2014). Therefore,

$$TBV_{\text{adjusted}} = TBV - \beta(ICV_{\text{raw}} - ICV_{\text{mean}})$$

Equation 3.2. Adjusted TBV

Note: TBV = total brain volume; ICV = intracranial volume. TBV_{adjusted} was calculated in accordance with Voevodskaya et al. (2014).

3.2.1.5 Graph Theory

Graph theory was first introduced in Chapter 1. Using the CONN toolbox, multiple graph theory metrics were adopted to measure for network characteristic differences between tested groups.

Specifically, the main effect differences were explored in Chapter 5. between CU and MCI participants, whilst stratifying further into A β status groups (CU A β -, CU A β +, MCI A β -, MCI A β +), and comparing functional connectivity “within” and “between” these two diagnostic categories: (1) CU A β - vs CU A β +, (2) MCI A β - vs. MCI A β +, (3) CU A β - vs. MCI A β -, and (4) CU A β vs. MCI A β +, and Chapter 7. between CU A β - vs. CU A β + sub-groups.

Briefly, the definitions for each graph theory metric used in this project are as follows (see “*CONN toolbox - Graphs [ROI-level]*”):

1. Degree and Cost: the number (degree) or proportion (cost) of edges from/to each node.
2. Average Path Distance: minimum number of edges traversed in an optimal path between each node.
3. Clustering Coefficient: the proportion of connected edges in the local neighbouring sub-graph for each ROI.
4. Global Efficiency: The average inverse distances between this node and all other nodes in the same graph.
5. Local Efficiency: The global efficiency of the neighbouring sub-graph of this node.

6. Betweenness Centrality: An alternative measure of node centrality within a graph – the proportion of times a node is part of the shortest path between any two pairs of nodes within a graph.

3.2.2 Statistics

All statistical analyses were run in SPSS (version 28.0; IBM Corp, 2021), Jamovi (version 2.5.6; The Jamovi Project, 2024), and SAS (version 17.0; SAS Institute Inc, 2021).

3.2.2.1 Descriptive Statistics

Participant data from both the ADNI-3 and OASIS-3 studies were summarised using descriptive statistics and illustrated using tables and figures. Various descriptive statistics, such as measures of central tendency (mean, median, and mode) and dispersion (e.g., range, standard deviation [*SD*]), were included.

3.2.2.2 Inferential Statistics

A series of inferential tests were conducted to measure correlations with non-normally distributed data (Spearman's rank), moderation, or reduction in dimensionality (PCA).

Significant *p*-values were set at $p < .05$ for all statistical tests.

3.2.2.2.1 Spearman's Rank Tests

Spearman's rank tests were used in Chapter 7. To justify their use, the non-normality of the collected OASIS-3 data was determined via visual inspection (histograms and Q-Q plots), running Shapiro-Wilk Tests (if $p < .05$, you reject the null hypothesis, indicating that the data significantly deviates from a normal distribution; Ghasemi & Zahediasl, 2012) and checking the skewness and kurtosis of distributions. Spearman's rank tests were run after PCA (see below; 3.2.2.2.3) to measure the correlations between AD biomarkers and functional connectivity principal components (PCs derived from PCA). See also Equation 3.3.

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

Equation 3.3. Calculation for Spearman's rank, whereby ρ = Spearman's rank correlation coefficient, n = the number of data pairs, and d^2 = the square of the difference in the ranks of the two variables for each data pair.

3.2.2.2.2 Moderation Analyses

The SPSS macro extension PROCESS (Hayes, 2012) was used for simple moderation analyses. The moderation model (Figure 3.10.) focused on testing whether localised A β and tau are moderators (M) between functional connectivity (X ; derived from ROI-to-ROI analyses) and multidomain cognitive performance (Y).

The PROCESS macro is also robust against outliers and non-normal data (no assumptions are made regarding the shape of the distribution) and is outlined in detail within Hayes' 2013 textbook, *"Introduction to Mediation, Moderation, and Conditional Process Analysis: A regression-based approach (2nd ed.)"*. Its robustness against outliers and non-normal data was a factor for consideration with both AD biomarker and functional connectivity data used within this study. PROCESS uses bootstrapping, which does not rely on normal distribution assumptions, and works by repeatedly resampling the data to create more reliable estimates and reduce the impact of outliers (Hayes, 2013).

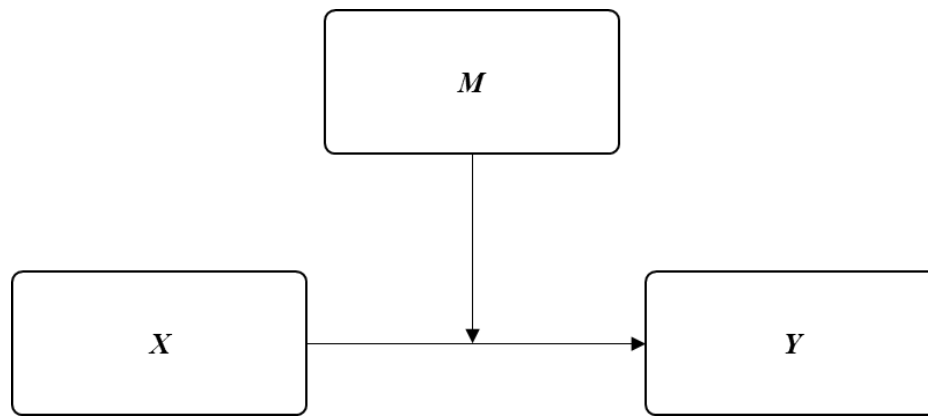


Figure 3.10. Simple moderation model

Note: M = Moderator (Amyloid or Tau); X = independent variable (Functional Connectivity); Y = dependent variable (Cognitive Domain).

3.2.2.2.3 PCA

In Chapter 7, PCA was conducted to reduce dimensionality by integrating the average functional connectivity strength for each cluster into a single PCA model.

An oblimin rotation was chosen due to functional connections often being highly correlated with one another (Jackson, 2005). The number of components generated was based on parallel analysis and confirmed by checking the scree plot. This allowed for visual interpretation of the appropriate number of PCs for follow-up analyses involving AD biomarkers for the next set of analyses in Chapter 7. Finally, Bartlett's test of sphericity (Bartlett, 1950) and Kaiser-Meyer-Olkin (described in "*Psychometrika*" by Kaiser, 1974) were used to measure the data's suitability for PCA.

3.2.2.2.4 Robust Linear Regression

Chapter 7 used robust linear regression due to various variables demonstrating non-normality and outliers. It is a form of regression analysis designed to overcome the limitations of traditional least squares regression (which can be heavily influenced by outliers and violations of statistical

assumptions) by assigning different weights to data points based on their residuals (see Malek-Ahmadi et al., 2024).

3.2.2.2.5 Multiple Test Corrections

Multiple corrections were conducted using Bonferroni correction (more conservative) and FDR (Benjamini-Hochberg (Benjamini & Hochberg, 1995; less conservative); see Equations 3.4. and 3.5. respectively.

$$\alpha_{\text{adjusted}} = \frac{\alpha}{m}$$

Equation 3.4. Bonferroni correction

Note: α_{adjusted} is the adjusted significance level for each test, α = the original significance level (.05). n = the number of comparisons or tests being performed.

Benjamini-Hochberg procedure is calculated as follows, given m hypotheses:

$$p_1, p_2, \dots, p_n$$

The corresponding p -values are then ordered – smallest to largest:

$$p_1 \leq p_2 \leq \dots \leq p_n$$

Next, the Benjamini-Hochberg critical value for each test is calculated using the following equation:

$$p_k \frac{k}{n} \times \alpha$$

Equation 3.5. Benjamini-Hochberg's critical value

Note: p_k = the k^{th} smallest p -value; n = total number of tests; k = rank of the p -value; and α = desired FDR threshold (in this case, .05).

3.3 Summary and Next Steps

For this project, two datasets - ADNI-3 and OASIS-3 - were utilised to conduct cross-sectional analyses using various approaches that can broadly be divided into “data-driven” and “hypothesis-driven”. These datasets were chosen due to their inclusion of resting-state fMRI, structural MRI, A β -PET, and tau-PET scans.

The ADNI-3 dataset included participants across the AD continuum (referred to in this project as CU, MCI, and DAT), whereas OASIS-3 focused on CU.

Regardless, all neuroimaging data were processed using the same software (CONN) for data pre-processing, denoising, and quality control checks. Additional imaging software was employed depending on requirements, e.g., FSL for custom brain imaging masks and Freeview for visualisation. SUVR and Centiloid metrics were used to quantify radiotracer uptake in PET imaging, and A β -PET status thresholds were established to classify participants based on A β accumulation.

The study's methodology integrates advanced imaging techniques and neuropsychological assessments to investigate the correlation between functional connectivity and AD biomarkers across AD stages.

Next, Chapters 4 to 7 will cover the results collected as part of this project, beginning with whole-brain ROI-to-ROI analyses with TFCE.

Chapter 4: Differences in Whole Brain Functional Connectivity Between AD Stages

4.1 Abstract

Background and Purpose: Patients with AD show differences in brain functionality compared to those at earlier stages of the AD spectrum (CU and MCI). The extent to which increased or decreased functional connectivity is present across the AD continuum may contribute to building our understanding of AD heterogeneity.

Methods: 252 newly enrolled older adults from ADNI-3 were included in this cross-sectional study (CU = 167, MCI = 68, and DAT = 17). Whole-brain ROI-to-ROI analyses were used to identify pairwise differences in functional connectivity and explore differences in functional connectivity between AD stages. TFCE was used for cluster-level inferences (false discovery rate [FDR] $p < .05$). Graph theory was also utilised using seven commonly used metrics to characterise the topological differences between groups.

Results: When comparing whole-brain functional connectivity patterns between CU and DAT participants, 20 clusters survived p -family wise error (FWE) correction $< .05$ (TFCE), comprising 72 statistically significant ROI-to-ROI connections. Fewer clusters were extracted when comparing MCI and DAT participants. Twelve clusters survived p -FWE $< .05$ (TFCE), comprising 44 ROI-to-ROI connections. No significant results were found between CU and MCI.

The right inferior frontal gyrus (pars triangularis) was the most frequently cited brain region, showing differences in functional connectivity between CU and DAT participants. The right inferior temporal gyrus (temporooccipital part) was often found when comparing MCI and DAT.

Furthermore, graph theory revealed betweenness centrality differences across all three group comparisons and average path length differences between CU and DAT and MCI and DAT.

Conclusions: No differences in functional connectivity were observed at earlier stages of AD (CU vs. MCI). However, many differences in functional connectivity were found when comparing CU vs. DAT participants and MCI vs. DAT participants. This could have implications for understanding the progression of AD and developing targeted interventions. Furthermore, betweenness centrality differences were observed across all group comparisons. This suggests its potential role as a sensitive measure to characterise topological differences in functional connectivity patterns across different

disease stages. Meanwhile, average path length may be more useful when comparing earlier (CU and MCI) vs. DAT participants. The extent to which average path length differences were present suggests a widespread reconfiguration of network structures that warrants further investigations.

4.2 Background

The human functional connectome represents the intricate network of connections within the brain (Sun et al., 2023). Advanced neuroimaging techniques like resting-state fMRI can reveal insights into the brain's organisational structure (Sun et al., 2023). One such measurement is functional connectivity. It refers to the temporal correlations between spatially distinct brain regions, reflecting how brain areas communicate during various tasks or in a state of rest (Friston, 2011). Understanding functional connectivity differences between groups (e.g., patients vs healthy controls) may aid in identifying the underlying neural mechanisms behind neurodegenerative diseases, such as AD.

The brain's functionality changes over the course of AD, both in their patterns of configuration and topography, as well as the strength of region-to-region signals (Wang et al., 2019). Determining where and to what extent these changes are present between AD stages may develop our understanding of disease progression (Wang et al., 2019). Prior research also describes changes in the brain's functional topology to shift towards increased modularity and randomness at later stages (Fathian et al., 2022). But these changes are complex, non-linear, and can demonstrate increases and decreases relative to other groups (Wang et al., 2019), and therefore require careful consideration of methodological choices.

Traditional ROI-based approaches - using pre-selected brain regions (*a priori*) - may overlook more complex connectivity patterns across the brain (Cole et al., 2010). To address this limitation, cluster-based functional connectivity analysis across the whole brain provides a data-driven method for detecting spatially contiguous networks of functional connectivity changes without needing *a priori* selection of brain regions (Venkataraman et al., 2009). Metzen et al. (2024) succinctly stated, "In the context of neurobiology, clustered connectivity indicates the existence of brain regions that constitute functionally coherent units with a high degree of within-unit information exchange".

However, due to the vast quantities of output when running whole-brain analyses, this chapter focused on investigating and characterising three facets of cluster-based functional connectivity analysis at the group level, which we termed "extent", "space", and "directions" of group-level functional connectivity

differences. Although these exact terms are not always used across studies, we noted that these themes were present across many studies adopting a cluster-based approach as described in the following ways:

1. “Extent”: In this context, it refers to the size and number of functional connectivity clusters showing significant differences between groups (suggesting greater disruptions in brain network integrity from CU [earliest stage included in this project] to DAT [latest stage included in this project]). Studies have shown a progressive increase in network disruptions between health controls, those with MCI and AD, with later stages exhibiting more widespread disruptions across progressively larger brain areas (Lama & Kwon, 2023). Using a cluster-based method, Lama and Kwon (2023), we can identify contiguous clusters of brain regions within networks that significantly differ between AD groups.
2. Next, “space” refers to the locations of these functional connectivity differences. Previous studies have identified many locations exhibiting functional connectivity disruptions and group-level differences. For example, Joshi et al. (2019) adopted a clustering approach to investigate functional connectivity between various resting-state networks. Increased resting-state functional connectivity was found specifically within the task-positive networks (Dorsal Attention and Executive Control networks) among those with AD, and these patterns robustly differentiate between those MCI and healthy controls (Joshi et al., 2019). Meanwhile, the Default Mode network-to-Dorsal Attention network functional connectivity is reduced compared to MCI and healthy controls (Joshi et al., 2019). Therefore, cluster-based analysis enables us to pinpoint the brain areas most strongly involved in the altered functional connectivity patterns between AD stages, offering insights into the spatial distribution of these differences.
3. Regarding “direction”, functional connectivity generally decreases progressively from CU to MCI to AD, reflecting network dysfunction (e.g., Jones et al., 2016; Singh et al., 2023). However, there is some evidence of (potentially) compensatory increases in functional connectivity between certain areas during early MCI stages, which may reflect adaptive

processes in response to neuronal changes, but the patterns of which are variable (Luo et al., 2022). For example, those with MCI (and evidence of sleep disorder) in the default mode network demonstrated weaker functional connectivity with the left middle frontal gyrus and right superior marginal gyrus (Luo et al., 2022). However, the Default Mode network showed stronger functional connectivity with the left parahippocampus, left precuneus and left middle temporal gyrus (Luo et al., 2022). Nevertheless, by examining the polarity of the connectivity changes (e.g., increased connectivity in one group, decreased in another), we can better understand how different groups' brain networks diverge regarding communication efficiency or synchronisation.

As mapping the human functional connectome presents a significant dimensionality problem due to thousands of connections being able to be measured, even at the macro-scale point of spatial resolution (Vidaurre, 2021), integrating robust, data-driven, statistical methods may help in improving sensitivity and specificity of the resulting outcomes; and when correcting for multiple comparisons, reducing type I error risk (Smith & Nichols, 2009). Ultimately, it ensures that one's findings are robust, reproducible, and scientifically sound.

4.2.1 Aims and Objectives

Therefore, by combining the analysis of functional connectivity group differences' extent, space, and direction using a cluster-based functional connectivity approach, we aimed to obtain a comprehensive picture of how neural communication patterns differ between AD groups: CU, MCI, and DAT. Given the high-dimensional nature of whole-brain analyses, TFCE was used to streamline the results and reduce the complexity of the output. Analyses utilised cluster-based functional connectivity analyses, with a specific focus on three factors: the 'extent' to which functional connectivity was different between AD stages, 'space' (where are these differences located?), and the 'directions' of effect (is functional connectivity higher or lower between each group comparison?) Finally, various graph theory measures were applied to better characterise the topological differences across AD stages.

4.3 Methods

4.3.1 Study Design

As described in Chapter 3, ADNI-3 was chosen for this chapter due to its multimodal sequencing study design (resting-state fMRI, structural MRI, and both an A β -PET and tau-PET) and the fact that this dataset uses a standardised imaging protocol for data acquisition.

4.3.2 Study Participants

Newly enrolled participants from the ADNI-3 study were included in cross-sectional analyses ($n = 252$). Male and female participants between the ages of 60 – 90 years of age were chosen based on data availability for all required data acquisition sequences for Chapters 4 – 6: resting-state fMRI (for functional connectivity analyses), structural MRI (to pair alongside resting-state fMRI data for spatial localisation purposes), and an A β -PET and tau-PET (the latter two scanning sequences were used in Chapters 5 and 6).

Inclusion for subsequent data analyses depended upon passing data quality checks at all stages: before pre-processing, after pre-processing, and after denoising.

4.4 Data Analysis

All brain imaging analyses were conducted within the CONN toolbox, with age, sex, and TBV being used as covariates of no interest.

Three group comparisons were conducted for each set of analyses (whilst controlling for age, sex, and TBV): CU vs. MCI, CU vs. DAT, and MCI vs. DAT. Cluster-based analyses were used to explore group-level differences in functional connectivity in terms of ‘extent’, ‘space’, and ‘direction’. Clusters of functional connectivity were identified as statistically significant and were selected based on strong functional connectivity. In the results section for this Chapter, it should be noted that statistical tests of individual connections within each cluster are not independent and, therefore, the statistical significance of these connections is overestimated.

4.4.1 Whole Brain ROI-to-ROI

Whole brain ROI-to-ROI analysis was conducted across three group comparisons, CU vs MCI, CU vs DAT, and MCI vs DAT, to explore group-level differences in functional connectivity across 164 ROIs (whole brain). This method was chosen to examine (a) whether group-level differences in functional connectivity were present across all group comparisons and (b), if so, where these changes were located. The resulting output was comprised of clusters (or groups) of functionally connected regions. In this context, a cluster is defined as a group of brain regions exhibiting similar activity patterns, and these regions are more strongly functionally connected within each cluster than outside (Baruzzi et al., 2023).

4.4.1.1 TFCE

Due to the large number of group-level functional connectivity differences between CU and DAT and MCI and DAT participants, TFCE (with 1000 permutations) was employed to reduce the number of connections and identify the key areas in which differences in functional connectivity were present between these group comparisons. Clusters are ordered using optimal leaf ordering (see Bar-Joseph et al., 2001).

As described in Chapter 3, TFCE enhances clusters based on the signal's size and intensity. Large, weak, and small, strong clusters are enhanced, allowing TFCE to be sensitive to a wide range of signal characteristics (Smith & Nichols, 2009). Unlike other clustering methods, it is threshold-free (e.g., unlike spatial pairwise clustering), and therefore, it does not require the input of an arbitrary threshold (Smith & Nichols, 2009).

4.4.2 Graph Theory

Lastly, graph theory characterised the topological differences in functional connectivity patterns between groups (at the ROI level; Sporns, 2018). Seven commonly used graph theory metrics: degree and cost, average path length, clustering coefficient, global efficiency, local efficiency, and betweenness centrality (see Latora & Marchiori, 2001; Achard & Bullmore, 2007).

4.5 Results

4.5.1 Demographic and Clinical Characteristics

The second-level group analysis included 252 newly enrolled ADNI-3 participants, 167 of whom were CU, 68 of whom were diagnosed with MCI, and 17 of whom were DAT.

Participants with DAT were older ($M = 77.74$ years [$SD = 6.63$] compared to CU ($M = 71.82$ years [$SD = 5.67$]) and MCI (74.96 years [$SD = 5.88$]). The CU cohort ($n = 167$) was comprised of more females ($n = 103$; 61.68%) compared to males ($n = 64$; 38.32%). However, the MCI and DAT cohorts were approximately equal in sample size among males. Specifically, the MCI cohort ($n = 68$) was comprised of 30 females (44.12%) and 38 males (55.88%), and the DAT cohort ($n = 17$) was comprised of eight females (47.10%) and nine males (52.94%). Furthermore, TBV for this sample was approximately equal between groups: the average TBV for CU participants was 1228.98 ml ($SD = 127.83$), and for MCI, it was slightly higher with an average TBV of 1258.42 ml ($SD = 131.88$). Lastly, among DAT participants, the TBV was also somewhat higher on average than CU participants (1242.17 ml [$SD = 183.30$]).

4.5.2 Group-Level Differences in Whole Brain ROI-to-ROI Functional Connectivity Analyses

Due to the large amount of data output generated from these analyses, the following information was included in-text: TFCE cluster information - number of significant functional connections, cluster TFCE, statistical significance (p -FDR and p -FWE), and spatial characteristics – which (significant and trending) functional connections were present within each cluster. Additional information was added to Appendices 4.1.1. and 4.1.2. Clusters were ordered by TFCE value (highest to lowest).

4.5.2.1 TFCE

No significant differences in whole-brain ROI-to-ROI functional connectivity were observed between CU and MCI participants. Suggesting that functional connectivity differences are not present between CU and MCI participants.

When comparing whole brain ROI-to-ROI functional connectivity between CU and DAT participants, 20 clusters, comprised of 95 ROI-to-ROI functional connections, were different between CU and DAT participants (Figure 4.1.). Seventy-two functional connections were statistically significant at $p < .05$ (75.79%). Compared to DAT, functional connectivity was higher among CU in 17 out of 20 (85%) of clusters. See Appendix 4.1.1 for a complete description of each cluster's functional connection.

Cluster 1 of 20: was comprised of seven functional connections. The number of significant functional connections = 7 out of 7 (100%), cluster TFCE = 101.21, p -FDR = .005, p -FWE = .003. This cluster showed a predominance of left-hemispheric functional connectivity involving regions such as the left lateral prefrontal cortex, left middle frontal gyrus, left anterior insula, and left frontal operculum. These connections highlight significant interaction between the Frontoparietal and Salience networks, with notable involvement of the frontal lobe and the anterior insula. This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 2 of 20: was comprised of two functional connections. The number of significant functional connections = 2 out of 2 (100%), cluster TFCE = 100.38, p -FDR = .005, p -FWE = .003, and consisted of substantial connections between the thalamus and the amygdala, involving both the left and right thalamus connecting to the left amygdala. This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 3 of 20: was comprised of three functional connections. The number of significant functional connections = 3 out of 3 (100%), cluster TFCE = 95.45, p -FDR = .005, p -FWE = .004, and was defined by significant connections involving the cingulate gyrus (posterior division), left temporal pole, left parahippocampal gyrus, and left thalamus. These connections include the posterior cingulate gyrus to the left temporal pole, the posterior cingulate gyrus to the left parahippocampal gyrus, and the left thalamus to the left parahippocampal gyrus. This cluster suggested functional connectivity being higher among CU participants, compared to DAT (CU > DAT).

Cluster 4 of 20: was comprised of two functional connections. The number of significant functional connections = 2 out of 2 (100%), cluster TFCE = 82.94, p -FDR = .006, p -FWE = .009, and consisted

of significant connections between the juxtapositional lobule cortex (formerly known as the supplementary motor cortex) and different parts of the Visual network. One functional connection was significant between the right juxtapositional lobule cortex and the Visual network (medial portion) and another between the left juxtapositional lobule cortex and the Visual network (left lateral portion). This cluster suggested functional connectivity being higher among DAT, compared to CU ($CU < DAT$).

Cluster 5 of 20: was comprised of two functional connections. The number of significant functional connections = 1 out of 2 (50%), cluster TFCE = 78.35, p -FDR = .006, p -FWE = .012, and consisted of one functional connection between the right pallidum and right temporal fusiform cortex (posterior division). This cluster suggested functional connectivity was higher among CU participants than among DAT participants ($CU > DAT$).

Cluster 6 of 20: was comprised of six functional connections. The number of significant functional connections = 6 out of 6 (100%), cluster TFCE = 75.61, p -FDR = .006, p -FWE = .020, and was characterised by significant functional connections between regions in the right frontal lobe and subcortical structures in the left hemisphere - including the left putamen and left pallidum specifically, between the right inferior frontal gyrus (both the pars triangularis and pars opercularis) and the right frontal pole to the left putamen and left pallidum. The Language network functional connections - centred in the right inferior frontal gyrus - were also functionally connected with the left putamen and left pallidum. This cluster suggested functional connectivity was higher among DAT, compared to CU ($CU < DAT$).

Cluster 7 of 20: was comprised of three functional connections. The number of significant functional connections = 3 out of 3 (100%), cluster TFCE = 74.42, p -FDR = .006, p -FWE = .021. This cluster included significant functional connections between the thalamus and the cerebellum. Specifically, it included functional connections between the right thalamus and the right cerebellum (crus one and crus 2) and from the left thalamus and the right cerebellum (crus 2). This cluster suggested functional connectivity was higher among CU participants than among DAT participants ($CU > DAT$).

Cluster 8 of 20: was comprised of five functional connections. The number of significant functional connections = 5 out of 5 (100%), cluster TFCE = 74.14, p -FDR = .006, p -FWE = .021, and included significant functional connections between the right inferior frontal gyrus (specifically the pars

triangularis) with both the right cerebellum (lobule 6) and left cerebellum (lobule 6). As well as the Language network (right inferior frontal gyrus) was functionally connected with the right cerebellum (lobule 6), left cerebellum (lobule 6), and vermis (lobule 8). This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 9 of 20: was comprised of eight functional connections. The number of significant functional connections = 5 out of 8 (62.50%), cluster TFCE = 72.76, p -FDR = .006, p -FWE = .022. This cluster was characterised by significant or trending functional connections between the right inferior frontal gyrus (pars opercularis) with the right angular gyrus, Frontoparietal network (right posterior parietal cortex), and Default Mode network (right lateral parietal cortex). As well as the right inferior frontal gyrus (pars triangularis) was functionally connected with the right angular gyrus, Frontoparietal network (right posterior parietal cortex), and Default Mode network (right lateral parietal cortex). Finally, one functional connection was significant between the Language network (right inferior frontal gyrus) and the Frontoparietal network (right posterior parietal cortex). This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 10 of 20: was comprised of one functional connection. The number of significant functional connections = 1 out of 1 (100%), cluster TFCE = 69.54, p -FDR = .006, p -FWE = .027, and consisted of a single statistically significant functional connection between the right middle temporal gyrus (temporooccipital part) and vermis (lobule 8). This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 11 of 20: was comprised of six functional connections. The number of significant functional connections = 6 out of 6 (100%), cluster TFCE = 69.10, p -FDR = .006, p -FWE = .028. This cluster comprised significant functional connections between the left planum polare, the precuneus, and the Default Mode network (posterior cingulate cortex). Furthermore, the left insular cortex was functionally connected with the precuneus and Default Mode network (posterior cingulate cortex). Finally, the Salience network (left anterior insula) was functionally connected with the precuneus and Default Mode network (posterior cingulate cortex). This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 12 of 20: was comprised of two functional connections. The number of significant functional connections = 2 out of 2 (100%), cluster TFCE = 67.79, p -FDR = .006, p -FWE = .031, and consisted of the right middle temporal gyrus (temporooccipital part) was significantly functionally connected with the right cerebellum (lobule 6) and the Cerebellar network (anterior portion). This cluster suggested functional connectivity was higher among CU participants compared to DAT participants (CU > DAT).

Cluster 13 of 20: was comprised of nine functional connections. The number of significant functional connections = 5 out of 9 (55.55%), cluster TFCE = 67.33, p -FDR = .006, p -FWE = .032. This cluster was made up of functional connections between the Language network (right inferior frontal gyrus), the right lateral occipital cortex (inferior division), and the Visual network (right lateral portion). The right inferior frontal gyrus (pars triangularis) was functionally connected with the right lateral occipital cortex (inferior division), the Visual network (right lateral portion), the right occipital fusiform gyrus, and the left occipital fusiform gyrus. This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 14 of 20: was comprised of two functional connections. The number of significant functional connections = 2 out of 2 (100%), cluster TFCE = 67.02, p -FDR = .006, p -FWE = .034. Both functional connections were statistically significant: the Dorsal Attention network (left intraparietal sulcus) and left paracingulate gyrus, and the left superior parietal lobule and left paracingulate gyrus. This cluster suggested functional connectivity was higher among CU participants compared to DAT participants (CU > DAT).

Cluster 15 of 20: was comprised of one functional connection. The number of significant functional connections = 1 out of 1 (100%), cluster TFCE = 66.14, p -FDR = .006, p -FWE = .036, and consisted of the cingulate gyrus (posterior division) and the Visual network (occipital portion). This cluster suggested functional connectivity was higher among CU participants compared to DAT participants (CU > DAT).

Cluster 16 of 20: was comprised of six functional connections. The number of significant functional connections = 4 out of 6 (66.66%), cluster TFCE = 64.73, p -FDR = .006, p -FWE = .043. This cluster was characterised by functional connectivity between the right inferior frontal gyrus (pars triangularis) and, right temporal fusiform cortex (anterior division), and right inferior temporal gyrus (anterior

division). As well as functional connections between the Language network (right inferior frontal gyrus) and right inferior temporal gyrus (anterior division), right temporal fusiform cortex (anterior division), and right middle temporal gyrus (anterior division). This cluster suggested functional connectivity was higher among CU participants than among DAT participants (CU > DAT).

Cluster 17 of 20: was comprised of five functional connections. The number of significant functional connections = 4 out of 5 (80%), cluster TFCE = 64.72, p -FDR = .006, p -FWE = .043, and was characterised by functional connections between the left putamen and right temporal fusiform cortex (anterior division) and right inferior temporal gyrus (anterior division). As well as a functional connection between the left pallidum and right middle temporal gyrus (anterior division) and a functional connection between the right pallidum and right inferior temporal gyrus (anterior division). This cluster suggested functional connectivity was higher among CU participants than DAT (CU > DAT).

Cluster 18 of 20: was comprised of 12 functional connections. The number of significant functional connections = 5 out of 12 (41.66%), cluster TFCE = 63.34, p -FDR = .006, p -FWE = .047. This cluster of the cingulate gyrus (anterior division) was functionally connected with the left temporal fusiform cortex (anterior division). The right paracingulate gyrus was functionally connected with the left temporal fusiform cortex (anterior division), left parahippocampal gyrus (anterior division) and left temporal pole. Furthermore, the left paracingulate gyrus was functionally connected with the left parahippocampal gyrus (anterior division). This cluster suggested functional connectivity was higher among DAT, compared to CU (CU < DAT).

Cluster 19 of 20: was comprised of nine functional connections. The number of significant functional connections = 4 out of 9 (44.44%), cluster TFCE = 63.12, p -FDR = .006, p -FWE = .048. For this cluster, the left supramarginal gyrus (anterior division) was functionally connected with the right cerebellum (lobule 10), brain stem, and right cerebellum (lobule 3). The Sensorimotor network (left lateral portion) was functionally connected with the right cerebellum (lobule 10). This cluster suggested functional connectivity was higher among CU participants compared to DAT participants (CU > DAT).

Cluster 20 of 20: was comprised of four functional connections. The number of significant functional connections = 4 out of 4 (100%), cluster TFCE = 62.76, p -FDR = .006, p -FWE = .048. The Visual

network (occipital portion) was functionally connected with the Default Mode network (left lateral parietal cortex), the Default Mode network (posterior cingulate cortex), the left lateral occipital cortex (superior division), and the precuneus. This cluster suggested functional connectivity was higher among CU participants compared to DAT participants (CU > DAT).

When comparing MCI and DAT, 12 clusters were found (44 out of 68 were statistically significant at $p < .05$; 64.71%; Figure 4.1.). Functional connectivity was higher among MCI participants (compared to DAT) in 9 of 12 clusters (75%). See Appendix 4.1.2 for a complete description of each cluster's functional connection.

Cluster 1 of 12: was comprised of 12 functional connections. The number of significant functional connections = 8 out of 12 (66.66%), cluster TFCE = 80.56, p -FDR = .014, p -FWE = .013. This cluster was comprised of functional connections between the left superior parietal lobule and the right inferior temporal gyrus (temporooccipital part), the right superior parietal lobule and the right inferior temporal gyrus (temporooccipital part), and the right inferior temporal gyrus (posterior division). The Dorsal Attention network (left intraparietal sulcus) was also functionally connected with the right inferior temporal gyrus (temporooccipital part) and the right inferior temporal gyrus (posterior division). Furthermore, the Dorsal Attention network (right intraparietal sulcus) was also functionally connected with the right inferior temporal gyrus (temporooccipital part) and the right inferior temporal gyrus (posterior division). Also, the right postcentral gyrus was functionally connected with the right inferior temporal gyrus (posterior division), and the right precentral gyrus was functionally connected to the right inferior temporal gyrus (temporooccipital part). This cluster suggested functional connectivity being higher among DAT, compared to MCI (MCI < DAT).

Cluster 2 of 12: was comprised of 13 functional connections. The number of significant functional connections = 5 out of 13 (38.46%), cluster TFCE = 80.06, p -FDR = .014, p -FWE = .014, and was comprised of the cingulate gyrus (anterior division) being functionally connected with the left temporal fusiform cortex (anterior division). Furthermore, the right paracingulate gyrus was functionally connected with the left parahippocampal gyrus (anterior division), left temporal fusiform cortex (anterior division), and left temporal pole. The left paracingulate gyrus was functionally connected with

the left parahippocampal gyrus (anterior division). This cluster suggested functional connectivity being higher among DAT, compared to MCI ($MCI < DAT$).

Cluster 3 of 12: was comprised of four functional connections. The number of significant functional connections = 3 out of 4 (75%), cluster TFCE = 73.49, $p\text{-FDR} = .014$, $p\text{-FWE} = .023$. The Sensorimotor network (superior division) was functionally connected with the right inferior temporal gyrus (temporooccipital part) and the right inferior temporal gyrus (posterior division). The left precentral gyrus is functionally connected with the right inferior temporal gyrus (temporooccipital part). This cluster suggested functional connectivity is higher among DAT participants than MCI participants ($MCI < DAT$).

Cluster 4 of 12: was comprised of three functional connections. The number of significant functional connections = 3 out of 3 (100%), cluster TFCE = 73.19, $p\text{-FDR} = .014$, $p\text{-FWE} = .023$. This cluster was comprised of functional connectivity between the left planum temporale and Frontoparietal network (left posterior parietal cortex); the left superior temporal gyrus (posterior division) and Frontoparietal network (left posterior parietal cortex); and the left superior temporal gyrus (posterior division) with the left angular gyrus. This cluster suggested functional connectivity was higher among MCI participants compared to DAT participants ($MCI > DAT$).

Cluster 5 of 12: was comprised of two functional connections. The number of significant functional connections = 2 out of 2 (100%), cluster TFCE = 71.45, $p\text{-FDR} = .014$, $p\text{-FWE} = .026$. The Dorsal Attention network was functionally connected with the left intraparietal sulcus and left paracingulate gyrus, and the left superior parietal lobule was functionally connected with the left paracingulate gyrus. This cluster suggested functional connectivity was higher among MCI participants than DAT participants ($MCI > DAT$).

Cluster 6 of 12: was comprised of two functional connections. The number of significant functional connections = 2 out of 2 (100%), cluster TFCE = 71.06, $p\text{-FDR} = .014$, $p\text{-FWE} = .026$. The left planum polare was functionally connected to the precuneus and Default Mode network (posterior cingulate cortex). This cluster suggested functional connectivity was higher among MCI participants than DAT participants ($MCI > DAT$).

Cluster 7 of 12: was comprised of three functional connections. The number of significant functional connections = 3 out of 3 (100%), cluster TFCE = 70.21, p -FDR = .014, p -FWE = .029. This cluster was comprised of functional connections between the Salience network (left anterior insula) and left lateral occipital cortex (superior division); the left insular cortex and the left lateral occipital cortex (superior division); and the left planum polare and the right lateral occipital cortex (superior division). This cluster suggested functional connectivity was higher among MCI participants than DAT participants (MCI > DAT).

Cluster 8 of 12: was comprised of nine functional connections. The number of significant functional connections = 6 out of 9 (66.66%), cluster TFCE = 67.97, p -FDR = .014, p -FWE = .034, and consisted of the right caudate being functionally connected with the left and right cerebellum (lobule 6), and vermis (lobules 7 and 8). Furthermore, the left caudate was functionally connected with the left cerebellum (lobule 6), Cerebellar network (anterior portion), and vermis (lobule 7). Finally, the left putamen was functionally connected with the left and right cerebellum (lobule 6). This cluster suggested functional connectivity being higher among MCI, compared to DAT (MCI > DAT).

Cluster 9 of 12: was comprised of three functional connections. The number of significant functional connections = 3 out of 3 (100%), cluster TFCE = 65.70, p -FDR = .014, p -FWE = .040. The right pallidum was functionally connected with the right lateral occipital cortex (inferior division) and right occipital fusiform cortex. The left pallidum is functionally connected with the right lateral occipital cortex (inferior division). This cluster suggested functional connectivity being higher among MCI, compared to DAT (MCI > DAT).

Cluster 10 of 12: was comprised of seven functional connections. The number of significant functional connections = 4 out of 7 (57.14%), cluster TFCE = 64.28, p -FDR = .014, p -FWE = .047. The Frontoparietal network (left lateral prefrontal cortex) was functionally connected with the Salience network (left anterior insula) and the left frontal operculum cortex. Furthermore, the left middle frontal gyrus was functionally connected with the Salience network (left anterior insula) and the left insular cortex. This cluster suggested functional connectivity being higher among MCI, compared to DAT (MCI > DAT).

Cluster 11 of 12: was comprised of seven functional connections. The number of significant functional connections = 2 out of 7 (28.57%), cluster TFCE = 64.05, p -FDR = .014, p -FWE = .048. This cluster comprised the left central opercular cortex functionally connected with the right hippocampus, right parahippocampal cortex (posterior division), and right amygdala. This cluster suggested functional connectivity being higher among DAT, compared to MCI ($MCI < DAT$).

Cluster 12 of 12: was comprised of three functional connections. The number of significant functional connections = 3 out of 3 (100%), cluster TFCE = 63.94, p -FDR = .014, p -FWE = .049. This cluster was composed of the left Heschl's gyrus being functionally connected with the Salience network (left supramarginal gyrus). As well as the left central opercular cortex being functionally connected with both the left supramarginal gyrus (posterior division) and the Salience network (left supramarginal gyrus). This cluster suggested functional connectivity was higher among MCI participants than DAT participants ($MCI > DAT$).

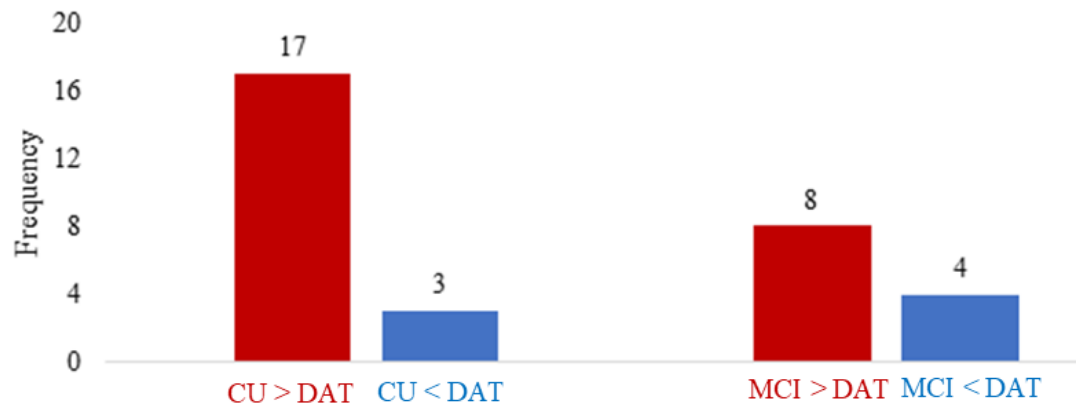


Figure 4.1. Bar chart showing the directions of effect between two main-effect group comparisons

Note: Positive (red) = cognitively unimpaired (CU) / mild cognitive impairment (MCI) functional connectivity (functional connectivity) was higher (>) than that of those with dementia due to Alzheimer's disease (DAT). Y-axis = frequency of clusters in either direction. Negative (blue) = functional connectivity was higher (>) among those with DAT, compared to CU / MCI functional connectivity. X-axis = group-level comparison to test whether functional connectivity among CU is higher than DAT (left) and functional connectivity among MCI is higher than DAT (right).

4.5.2.1.1 Spatial Properties of TFCE Clusters

When comparing functional connectivity between CU and DAT participants, 17 out of 20 clusters (85%) showed higher functional connectivity in the CU group compared to the DAT group (CU > DAT). Similarly, when comparing MCI and DAT participants, 8 out of 12 clusters (66.66%) indicated higher functional connectivity in the MCI group compared to the DAT group (MCI > DAT). Next, across all 20 clusters, comparing whole-brain functional connectivity patterns between CU and DAT participants revealed differences in functional connectivity in 59 out of 164 brain regions (35.98%). Similarly, when comparing MCI and DAT participants, 48 out of 164 brain regions (29.27%) showed differences in functional connectivity.

The right inferior frontal gyrus (pars triangularis) exhibited the most altered functional connections between CU and DAT participants, with 13 connections identified (see Figure 4.2. and Table 4.1.). This region was functionally connected with the left putamen and left pallidum (in Cluster 6 of 20); the right and left cerebellum (in Cluster 8 of 20); the right angular gyrus, the frontoparietal network (right posterior parietal cortex), and the default mode network (right lateral parietal cortex) (in Cluster 9 of 20); the right lateral occipital cortex (inferior division), the visual network (right lateral portion), and the right and left occipital fusiform gyrus (in Cluster 13 of 20); as well as the right temporal fusiform cortex (anterior division) and the right inferior temporal gyrus (anterior division) (in Cluster 16 of 20). The next most altered region was the right inferior frontal gyrus, part of the language network, with 11 altered connections.

In the comparison between MCI and DAT participants, the right inferior temporal gyrus (temporo-occipital part) showed the most altered functional connections, with seven connections identified (see Figure 4.3. and Table 4.2.). This region was functionally connected with the left superior parietal lobule, the dorsal attention network (left and right intraparietal sulcus), the right superior parietal lobule, and the right precentral gyrus (in Cluster 1 of 12), as well as the sensorimotor network (superior division) and the left precentral gyrus (in Cluster 3 of 12). The left central opercular cortex was the next region with the most altered functional connections, with five connections identified

CU vs. DAT

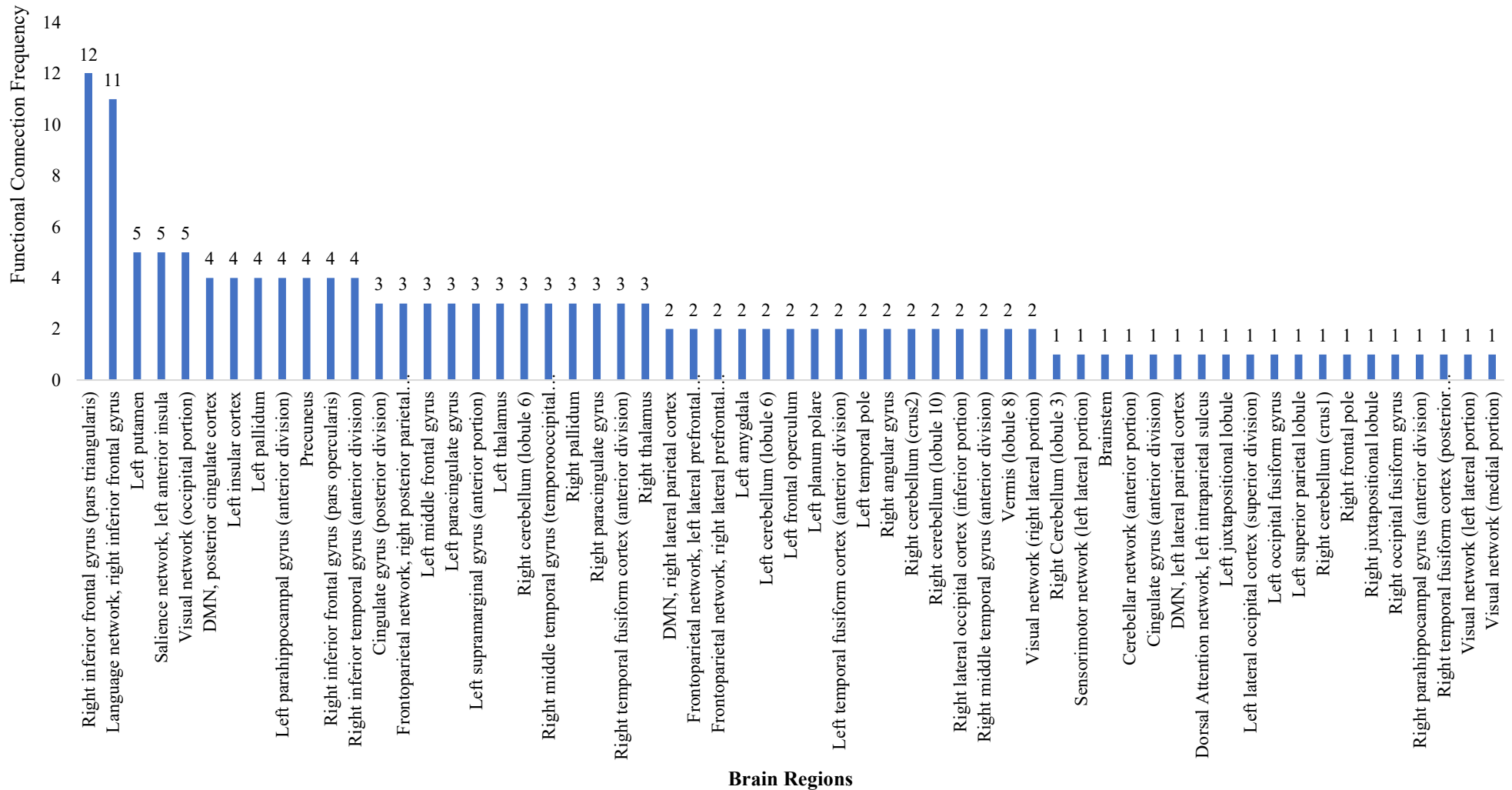


Figure 4.2. Bar chart showing the frequency of brain regions showing alterations in functional connectivity between CU and DAT participants

Note: Y-axis = frequency; X-axis = brain region. DMN = Default Mode network. CU = cognitively unimpaired; DAT = dementia due to AD.

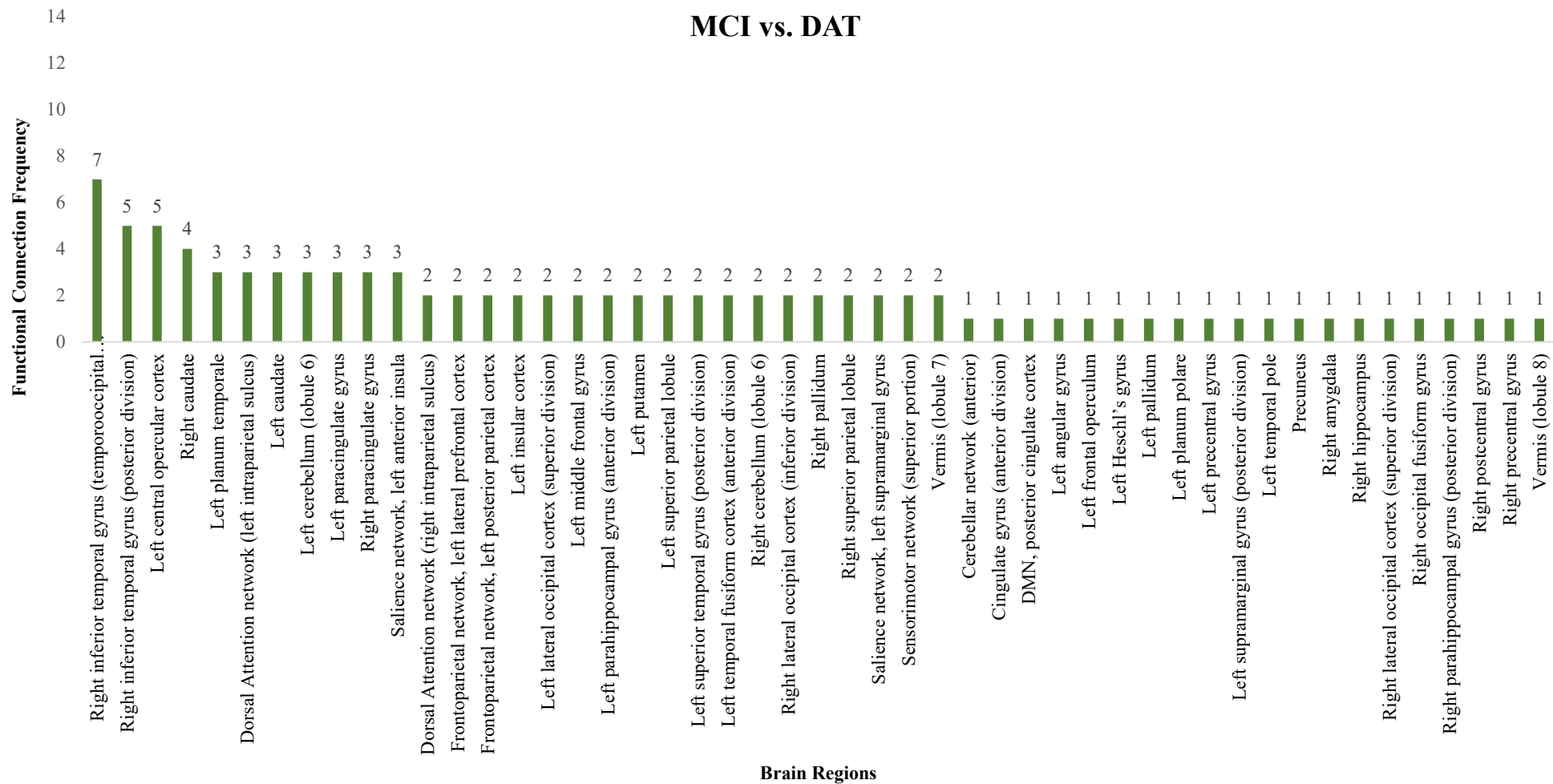


Figure 4.3. Bar chart showing the frequency of brain regions showing alterations in functional connectivity between those with MCI and DAT participants

Note: Y-axis = frequency; X-axis = brain region. MCI = mild cognitive impairment; DAT = dementia due to Alzheimer's disease.

Table 4.1. Surviving Clusters For CU > DAT Group-Level Comparison Using TFCE

Cluster #.	Connections* (%)	TFCE	<i>p</i> -FDR	<i>p</i> -FWE
1	7 / 7 (100)	101.21	.005	.003
2	2 / 2 (100)	100.38	.005	.003
3	3 / 3 (100)	95.45	.005	.004
4	2 / 2 (100)	82.94	.006	.009
5	1 / 2 (50)	78.35	.006	.012
6	6 / 6 (100)	75.61	.006	.020
7	3 / 3 (100)	74.42	.006	.021
8	5 / 5 (100)	74.14	.006	.021
9	5 / 8 (62.50)	72.76	.006	.022
10	1 / 1 (100)	69.54	.006	.027
11	6 / 6 (100)	69.10	.006	.028
12	2 / 2 (100)	67.79	.006	.031
13	5 / 9 (55.55)	67.33	.006	.032
14	2 / 2 (100)	67.02	.006	.034
15	1 / 1 (100)	66.14	.006	.036
16	4 / 6 (66.66)	64.73	.006	.043
17	4 / 5 (80)	64.72	.006	.043
18	5 / 12 (41.66)	63.34	.006	.047
19	4 / 9 (44.44)	63.12	.006	.048
20	4 / 4 (100)	62.76	.006	.048
Significant Connections	72 / 95 (75.79)			

Notes: Clusters are ordered using optimal leaf ordering for hierarchical clustering (Bar-Joseph et al., 2001). CU = cognitively unimpaired; DAT = dementia due to Alzheimer's disease; TFCE = threshold-free cluster enhancement; FDR = false discovery rate; FWE = family-wise error (rate). CU: *n* = 167; AD: *n* = 17. *Individual Region of interest (ROI)-to-ROI pairwise connection significant to at least FDR-*p* < .05.

Table 4.2. Surviving Clusters For MCI > DAT Group-Level Comparison Using TFCE

Cluster #.	Connections* (%)	TFCE	<i>p</i> -FDR	<i>p</i> -FWE
1	8/12 (66.66)	80.56	.014	.013
2	5/13 (38.46)	80.06	.014	.014
3	3/4 (75)	73.49	.014	.023
4	3/3 (100)	73.19	.014	.023
5	2/2 (100)	71.45	.014	.026
6	2/2 (100)	71.06	.014	.026
7	3/3 (100)	70.21	.014	.029
8	6/9 (66.66)	67.97	.014	.034
9	3/3 (100)	65.70	.014	.040
10	4/7 (57.14)	64.28	.014	.047
11	2/7 (28.57)	64.05	.014	.048
12	3/3 (100)	63.94	.014	.049
Significant Connections		44 / 68		

Notes: Clusters are ordered using optimal leaf ordering for hierarchical clustering (Bar-Joseph et al., 2001). MCI = mild cognitive impairment; DAT = dementia due to Alzheimer's disease; TFCE = threshold-free cluster enhancement; FDR = false discovery rate; FWE = family-wise error (rate). MCI: $n = 68$; AD: $n = 17$. * Individual Region of interest (ROI)-to-ROI pairwise connection significant to at least FDR- $p < .05$.

4.5.2.2 Results Summary

The whole-brain ROI-to-ROI functional connectivity analysis results revealed no significant differences between CU and MCI participants, suggesting similar functional connectivity patterns between these two groups. However, significant differences were found when comparing CU participants with those with DAT, with 20 clusters comprising 95 ROI-to-ROI connections showing significant functional connectivity differences, 73 of which were statistically significant. Notably, 85% of these clusters exhibited higher functional connectivity in CU participants compared to DAT. Additionally, comparisons between MCI and DAT participants revealed 12 clusters with significant differences in functional connectivity, with 64.71% of the connections being statistically significant. Among these, functional connectivity was higher in MCI participants in 75% of the clusters. These findings suggest a progressive decline in functional connectivity from CU to MCI to DAT, with the most pronounced differences observed between CU and DAT participants.

A visual depicting the patterns of these functional connections between both group comparisons can be found in Figures 4.4. - 4.6.

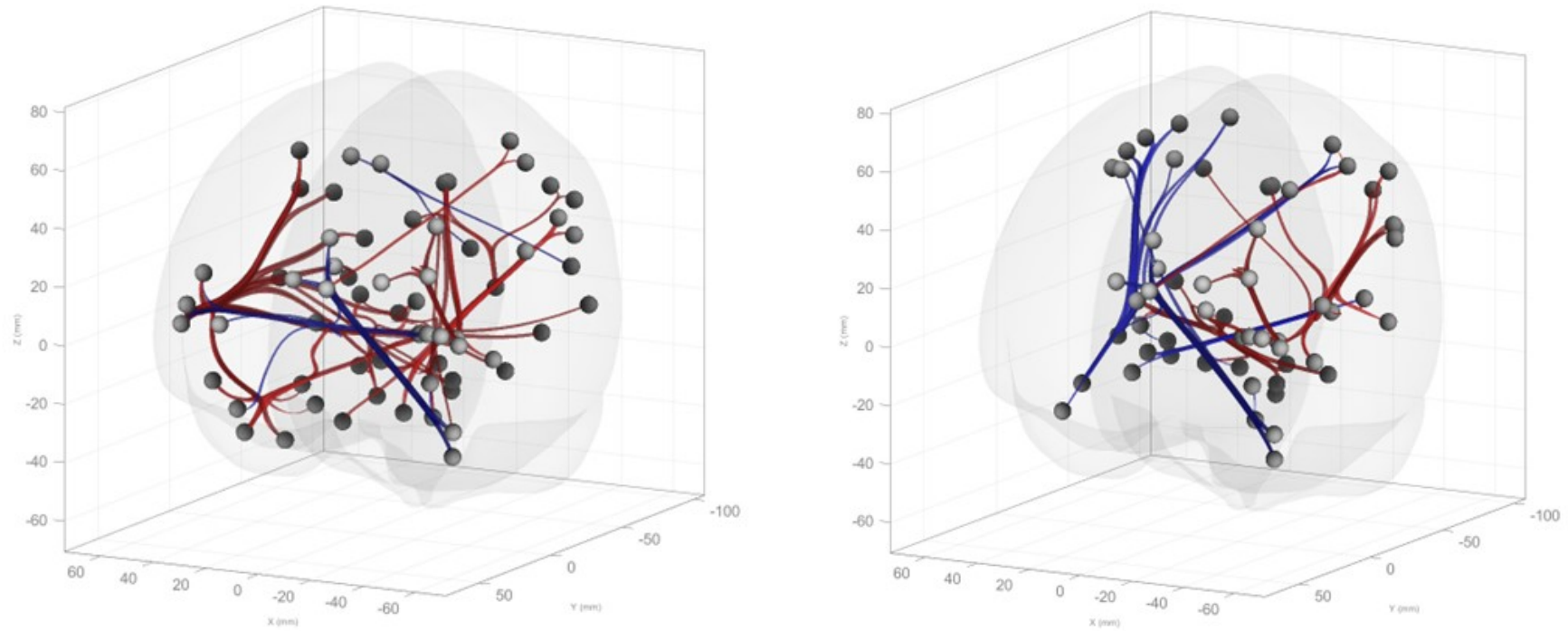


Figure 4.4. Three-dimensional glass brains depict mostly decreased functional connectivity at later stages

Note: *Left*: cognitively unimpaired (CU) functional connectivity > DAT. 72 / 95 region-of-interest (ROI)-ROI pairwise connections were significant to false discovery rate (FDR) $p < .05$.

Right: Mild cognitive impairment (MCI) functional connectivity > DAT. 44 / 68 ROI-to-ROI pairwise connections were significant to FDR $p < .05$.

Red = positive effects CU / MCI > DAT functional connectivity; Blue = negative effects DAT > CU / MCI functional connectivity.

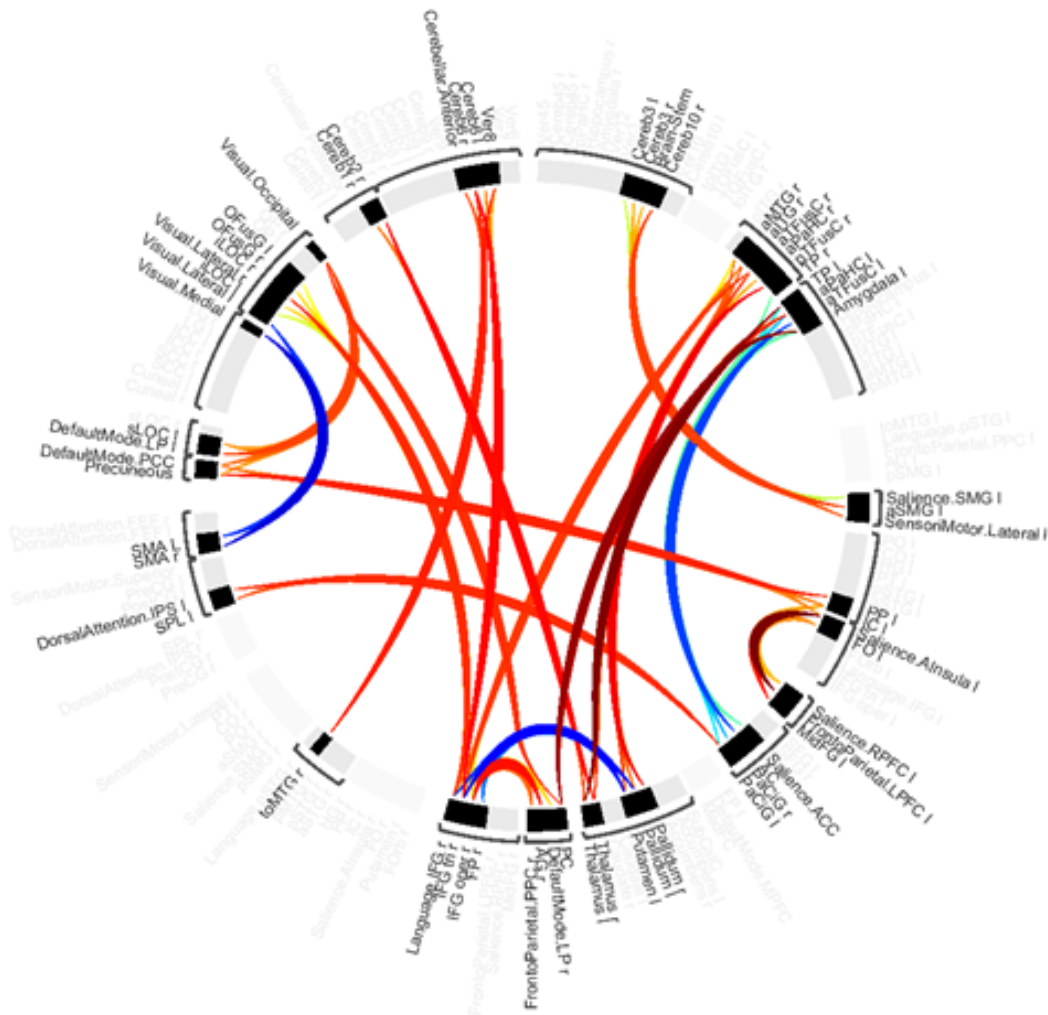


Figure 4.5. A connectomic ring showing statistically significant functional connectivity between brain regions for CU vs DAT

Note: Cognitively unimpaired (CU, $n = 167$) functional connectivity > dementia due to Alzheimer's Disease (DAT, $n = 17$).

Red = CU functional connectivity > DAT functional connectivity (denoting decreased functional connectivity among AD); **Blue** = CU functional connectivity < DAT functional connectivity (denoting increased functional connectivity among DAT).

Seventy-three statistically significant regions of interest (ROI)-to-ROI displayed.

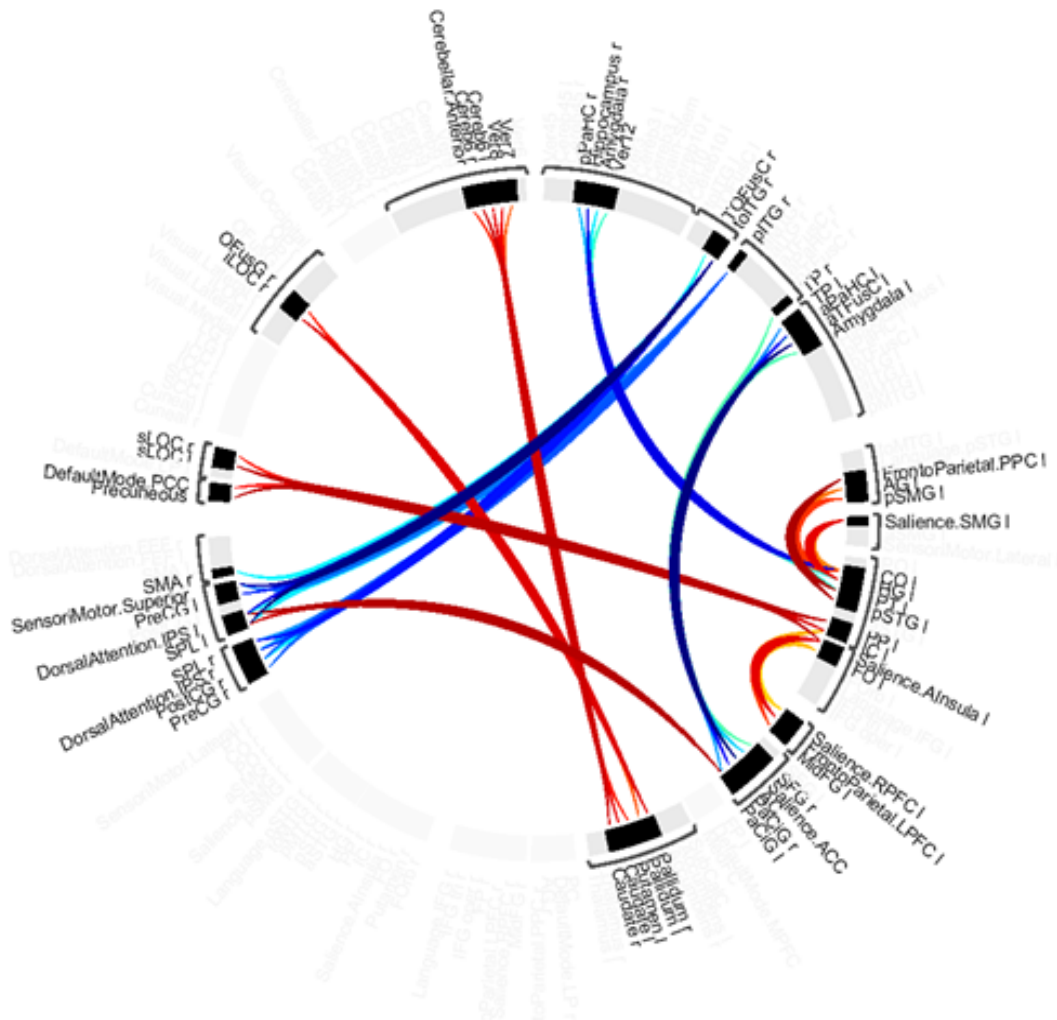


Figure 4.6. A connectomic ring showing statistically significant functional connectivity between brain regions for MCI vs DAT

Note: Mild cognitive impairment (MCI, $n = 68$) functional connectivity > dementia due to Alzheimer's Disease (DAT, $n = 17$).

Red = MCI functional connectivity > DAT functional connectivity (denoting decreased functional connectivity among DAT); **Blue** = MCI functional connectivity < DAT functional connectivity (denoting increased functional connectivity among DAT).

Forty-four statistically significant regions of interest (ROI)-to-ROI displayed.

4.5.3 Whole Brain Differences in Graph Network Properties

Seven graph theory measures were employed for three group comparisons: CU vs. MCI, CU vs. DAT, and MCI vs. DAT (see Table 4.3.).

Betweenness centrality was found to be significantly different within one node (right putamen) between CU and MCI participants: right putamen: $T(249) = -3.74$, p -uncorrected $<.001$, p -FDR = .037. No other significant differences were found with any other graph theory measures.

Betweenness centrality and average path length significantly differed between CU and DAT participants, with 12 nodes for betweenness centrality and 141 for average path length.

Similarly, when comparing all graph theory metrics between MCI and DAT participants, betweenness centrality and average path length significantly differed between them, specifically, 11 nodes for betweenness centrality and 118 for average path length.

In summary, betweenness centrality differences were present across all three group comparisons. Still, many more differences in average path length were present when comparing CU and DAT and MCI and DAT participants.

Table 4.3. Summary of Results for Group-Level Analyses at Whole-Brain Level

Cluster-based Inferences	CU vs. MCI		CU vs. DAT		MCI vs. DAT	
	TFCE	Graph Theory	TFCE	Graph Theory	TFCE	Graph Theory
<i>Extent</i>	No significant differences.	Betweenness centrality: 1 node.	20 clusters: 95 ROI-to-ROI connections.	Betweenness centrality: 12. Average path length: 141.	12 clusters: 44 ROI-to-ROI connections.	Betweenness centrality: 11 times. Average path length: 118 times.
<i>Space</i>	No significant differences.	Right putamen only.	Differences in functional connectivity in 59 out of 164 brain regions. Right inferior frontal gyrus (pars triangularis) was most cited.	Vast areas were significantly different between CU and DAT.	Differences in functional connectivity in 48/164 brain regions. Right inferior temporal gyrus (temporooccipital part) was most cited.	Vast areas were significantly different between MCI and DAT.
<i>Direction</i>	No significant differences.	Betweenness centrality: MCI > CU: 1 time. MCI < CU: 0.	CU > DAT: 17 times. CU < DAT: 3 times.	Betweenness centrality: CU > DAT: 0. Betweenness centrality: CU < DAT: 12 times. Average path length: CU > dementia due to DAT: 0. Average path length: CU < DAT: 141 times.	MCI > DAT: 8 times. MCI < DAT: 4 times.	Betweenness centrality: CU > DAT: 0. Betweenness centrality: CU < DAT: 11 times. Average path length: CU > DAT: 0. Average path length: CU < DAT: 118 times.

Notes. CU = cognitively unimpaired; MCI = mild cognitive impairment; DAT = dementia due to Alzheimer's disease; TFCE = threshold-free cluster enhancement; ROI = region of interest; CU / MCI > DAT = functional connectivity higher among CU / MCI participants compared to DAT.

4.6 Discussion

4.6.1 Summary

This chapter explored and investigated group-level whole-brain functional connectivity differences across three stages: CU, MCI, and DAT. To manage the large volume of data and resulting output, TFCE was applied to streamline the analysis. No significant functional connectivity differences were found between CU and MCI participants. However, comparing CU to DAT revealed 20 clusters with 95 ROI-to-ROI functional connections, with 59 of 164 regions showing functional connectivity differences. The right inferior frontal gyrus (pars triangularis) was most notable, cited 13 times, and 17 of the 20 clusters indicated higher functional connectivity in CU than in DAT. For the MCI vs. DAT comparison, 12 clusters with 68 functional connections were identified, with the right inferior temporal gyrus (temporooccipital part) showing the most frequent differences, cited seven times. Eight of these clusters suggested higher functional connectivity in MCI compared to DAT.

Graph theory analysis revealed higher betweenness centrality in the right putamen for MCI compared to CU and significant differences in betweenness centrality across 12 nodes (CU vs. DAT) and 11 nodes (MCI vs. DAT), with higher DAT values compared to CU and MCI. Average path length differences were noted in 141 nodes (CU vs. DAT) and 118 nodes (MCI vs. DAT), with higher DAT values than CU and MCI. No other group-level differences were observed for any other graph theory metric.

Overall, the results highlight significant changes in functional connectivity and network topology, demonstrating distinct group-level patterns, most notably when comparing CU vs DAT and MCI vs DAT participants.

Together, these findings highlight how alterations in functional connectivity patterns are statistically significant when comparing CU with DAT and MCI with DAT. These insights contribute to a deeper understanding of how DAT affects functional brain connectivity and network organisation.

4.6.2 No Differences in Whole-Brain Functional Connectivity Between Earlier AD Stages

No significant functional connectivity differences were observed between CU and MCI participants, suggesting that functional connectivity alterations may become more pronounced as the disease progresses (e.g., Lama & Kwon, 2023).

Also, MCI is a highly heterogeneous group that includes individuals at varying stages of cognitive decline, ranging from early-stage to late-stage MCI (Lee et al., 2021). This variability within the group could obscure functional connectivity differences between CU individuals and those with MCI, as previous research has found differences in functional connectivity patterns between those at the earlier vs. later stages of MCI (Kang et al., 2021). Therefore, the variability in functional connectivity strength within those with MCI could cancel out or nullify any overall group-level differences when compared to CU participants. This heterogeneity may pose a challenge for detecting functional connectivity changes, as averaging across such a mixed population may mask underlying differences.

4.6.3 Key Brain Regions Showing Most Differences Between Groups

The two brain regions showing the most frequent altered functional connections between CU and DAT, and MCI and DAT, were the right inferior frontal gyrus (pars triangularis) and right inferior temporal gyrus (temporooccipital part), respectively.

When comparing CU and DAT participants, the right inferior frontal gyrus (pars triangularis) was most frequently cited as exhibiting alterations in functional connectivity with other regions (including the left putamen, left pallidum, right and left cerebellum [lobule 6], right angular gyrus, Frontoparietal network, posterior cingulate cortex [trending significance], right lateral occipital cortex [inferior division], Visual network [right lateral portion, right occipital fusiform gyrus, left occipital fusiform gyrus [trending significance], right temporal fusiform cortex [anterior division], and right inferior temporal gyrus [anterior division; trending significance]).

The right inferior frontal gyrus has been largely cited as a brain region instrumental in response inhibition (Boen et al., 2022).

The right inferior frontal gyrus (pars triangularis) showed differences in functional connectivity among CU, compared to DAT, with 13 other regions. In “*Neuroanatomy, Putamen*”, the left putamen and pallidum are subcortical regions involved in many functions, including motor control and cognitive processing (Ghandili & Munakomi, 2023). Also, the cerebellum (e.g., lobule 6) has been found to subserve both motor coordination and cognitive functions (Koziol et al., 2014). The angular gyrus is connected with various mental processes such as language, memory retrieval, and attention (Seghier, 2013). Sub-regions of the Frontoparietal network are involved in multiple cognitive areas, including executive functions, attention, and working memory (Marek & Dosenbach, 2018). The posterior cingulate cortex is connected with roles such as memory retrieval (Leech & Sharp, 2014). At the same time, brain regions such as the lateral occipital cortex, Visual network, occipital fusiform gyrus, temporal fusiform cortex, and inferior temporal gyrus are linked to various visual-based processes (Miyashita, 1993; Nagy et al., 2012; Weiner & Zilles, 2016).

Furthermore, when comparing CU and DAT participants, the right inferior temporal gyrus (temporooccipital part) was most frequently cited as exhibiting alterations in functional connectivity with other regions.

The inferior temporal gyrus has been linked to certain cognitive processes, such as visual perception (Miyashita, 1993). The inferior temporal gyrus - specifically the temporooccipital part – demonstrated differences in functional connectivity between MCI and DAT participants with the following regions: The superior parietal lobule has been cited as supporting multiple functional processes as a “highly heterogeneous” region, including visuomotor and observational processes, attention, working memory, and reasoning (Wang et al., 2015). Furthermore, Grefkes and Fink’s 2005 review described the left and right intraparietal sulci (sub-regions of the Dorsal Attention network) being involved in visuomotor and attentional processes. The Sensorimotor network supports the integration of sensory information and coordinating motor functions (Wolpert & Miall, 1996). Finally, the precentral gyrus controls voluntary motor movements as outlined in a textbook by Banker and Tadi (2023).

In summary, when comparing functional connectivity between CU and DAT, the right inferior frontal gyrus (pars triangularis) suggests disrupted functional connectivity with several regions involved in multiple cognitive processes, such as motor control, visual processing, memory, and executive functions.

4.6.4 Monitoring Disease Progression

Whole-brain functional connectivity was found to show significant differences between 2 out of 3 AD group comparisons. Therefore, this begs the question of whether functional connectivity could be used to monitor disease progression at the mid to late stages of AD. Evidence to support functional connectivity in this manner was provided by Mondragón et al. (2021), demonstrating distinctive features between stable- and progressive MCI. Those with stable MCI were not found to have progressed to AD, and those with progressive MCI did. The researchers found the Default Mode and Salience networks (within and between these connections) to have significant and consistent differences between stable- and progressive MCI subtypes across multiple time points.

4.6.5 Potential Compensatory Mechanisms

Early-MCI participants demonstrated slightly decreased functional connectivity compared to healthy controls, while late-MCI and mild-AD participants presented increased functional connectivity in several regions (Penalba-Sánchez et al., 2023). The researchers theorised that AD pathology is less dispersed in early MCI, whereby the brain configuration is similar to healthy controls. Still, when the pathology advances and participants reach the late MCI and AD stages, the brain might attempt to compensate against this pathology by compensating and recruiting alternative paths to maintain functionality (Penalba-Sánchez et al., 2023). This, therefore, illustrates a non-linear connectivity pattern, starting at an optimal state of functional connectivity among healthy controls, followed by a slight decrease among early-MCI, and enhancement between several regions at the late-MCI and mild-AD stages (Penalba-Sánchez et al., 2023). Increased functional connectivity that sometimes occurs at

the beginning of many neurodegenerative diseases may be followed by decreased functional connectivity between functional pathways that are consequently associated with cognitive decline as the disease progresses (Marek & Dosenbach, 2018). More specifically, in the context of AD stages, those at the late-MCI stage and those at the beginning of AD (e.g., the ‘mild’ phase) may demonstrate widespread rewiring in attempts for the brain to maintain cognitive function. Still, this adaptive response only works in the short term (Bonanni et al., 2020). “Hyperconnectivity [increased functional connectivity] could be therefore interpreted as an early step in the mechanism of progressive neural degeneration” (Bonanni et al., 2020).

Recently, Hoehn & Aswendt (2023) asked whether this increased functional connectivity was a maladaptive process or an element of resilience, and they postulated that increased functional connectivity could be considered a compensatory mechanism embedded within the brain’s resilience capacity. They went on to state that animal studies involving amyloidosis and tau mouse models (as a representative of dementia) confirm the presence of increased functional connectivity, followed by network disruption. Increased functional connectivity is typically seen in early-stage disease, while late-stage disease results in decreased functional connectivity, therefore representing a dynamic shift in the brain’s adaptive response to injury (Hoehn & Aswendt, 2023).

It is important to note that studies such as Penalba-Sánchez et al. (2023) used multiple methods, including Pearson’s correlation, sliding-windows correlation analysis, and point process analysis. The latter two are considered advanced and ‘novel’. They were adopted to mitigate against one limitation of traditional mass univariate functional connectivity analysis: its sensitivity to residual noise. More advanced techniques may be necessary to maximise the sensitivity in detecting true effects.

4.7 Conclusions and Next Steps

The functional connectivity analysis highlights a clear gradient of functional connectivity differences across stages. The absence of significant functional connectivity differences between CU and MCI suggests that early cognitive impairment may not yet manifest in significant connectivity disruptions. In contrast, the marked differences in functional connectivity between CU and DAT and between MCI and DAT underline the progressive nature of functional connectivity loss across stages. However, it is important to note that the number of connections identified in these comparisons presents a significant challenge for subsequent analyses. With 95 ROI-to-ROI connections in the CU vs. DAT comparison and 68 connections in the MCI vs. DAT comparison, the vast number of statistically significant results (even with TFCE) complicates the interpretation and further analysis. Careful consideration is required to avoid numerous methodological and interpretability pitfalls, such as multiple comparisons and false positives.

These findings support the utility of functional connectivity measures in distinguishing between different stages. However, the volume of functional connections necessitates more advanced statistical methods to navigate this dimensionality issue while ensuring reliability and clinical applicability.

Therefore, despite employing a conservative means to reduce the number of functional connections in a spatially meaningful way, the resulting number of connections still present post-TFCE warrants an alternative approach. In Chapter 5, a supervised machine learning method was utilised - with the same group comparisons - to isolate functional connections that explain the most variance between groups.

Chapter 5: Using a Data-Driven Approach to Identify and Extract Key Regions of Functional Connectivity Variability Between AD Stages

5.1 Abstract

Background and Purpose: AD is a progressive neurodegenerative condition characterised by widespread brain changes. Examining functional connectivity across AD stages can reveal valuable insights into the brain's changing functional architecture. This chapter aimed to extract functional connections demonstrating group-level differences across CU, MCI, and DAT groups.

Methods: This chapter utilised participant data from the ADNI-3 cohort, focusing on participants aged 60 - 90 years, and categorised as CU ($n = 167$), MCI ($n = 68$), or DAT ($n = 17$).

Due to the high-dimensional output of whole-brain ROI-to-ROI with TFCE (Chapter 4), we adopted an alternative approach using whole-brain Multivariate Pattern Analysis. This method identified "seed" regions that explained the most variance between AD stages, using three group comparisons (1. CU vs MCI, 2. CU vs DAT, and 3. MCI vs DAT) for subsequent seed-based connectivity analyses.

Results: In the CU and DAT group comparison, the left thalamus and precuneus were identified as regions that explained the most variance and were then extracted as seed regions. In the MCI and DAT group comparison, key areas included the left thalamus, precuneus, and right and left portions of the superior frontal gyrus. Both group comparisons showed mixed patterns of increased and decreased functional connectivity among CU / MCI compared to DAT. No significant differences were found between CU and MCI.

Further, stratification into four A β sub-groups (CU A β -, CU A β +, MCI A β -, and MCI A β +) found no differences in functional connectivity using whole-brain ROI-to-ROI with TFCE (Chapter 4) or Multivariate Pattern Analysis (current chapter / Chapter 5).

Further supplementary analyses were conducted at a small spatial scale – network level. Here, we found statistically significant differences between CU and MCI A β subgroups.

Graph theory revealed group-level differences in average path length only.

Conclusions: The observed patterns of altered functional connectivity involving the left thalamus, precuneus, and frontal gyri may support their significance in AD progression and pathophysiology. These findings suggest that these regions warrant further investigation, particularly in studies exploring therapeutic interventions targeting these areas.

5.2 Background

Pathological biomarkers amyloid (A), tau (T), and neurodegeneration (N) form the “AT[N]” framework for AD (Jack et al., 2016) and have been instrumental in developing our understanding of this disease. Despite decades of extensive research, however, an effective cure for AD has not been developed. This may be partly attributed to the disease’s considerable heterogeneity, as individual differences in clinical phenotypes cannot be explained purely by AT[N] biomarkers alone (Dubois et al., 2021). In response, research has branched into other avenues - away from a strictly pathological-based approach - to explore alternative mechanisms underlying AD. One promising avenue involves investigating functional connectivity differences across AD stages using resting-state fMRI. This approach offers insights into the brain’s changing functional architecture during disease progression.

Yu et al. (2021) proposed that, during AD development, the sequence of pathological events begins with A β deposition, which drives changes in the brain’s functional connectome in the early stages of the disease. This hypothesis aligns with earlier seminal work by Buckner et al. (2009), who found that A β preferentially accumulated at cortical hubs within the Default Mode network. These findings are supported by other studies, whereby A β pathology was associated with decreased Default Mode functional connectivity being consistently found among those during the preclinical AD stage (Sperling et al., 2009) and through to those with early-onset AD (Lehmann et al., 2013).

Functional connectivity has been proposed as a potential biomarker to assess AD risk (Jalilianhasanpour et al., 2019). While it is increasingly used as a tool to measure functional brain changes, its adoption faces significant challenges. These include disease heterogeneity, individual differences (Zhang et al., 2021), and methodological limitations. For instance, traditional mass univariate analysis is affected by the “curse of dimensionality”, in which analysing each functional connection may be unpractical (Nieto-Castañón, 2022). Such analyses may inflate the risk of making type I errors (as indicated in a comparative review by Nichols & Hayasaka, 2003), neglect spatial correlations (Worsley & Friston, 1995), and overlook distributed patterns (Weaverdyck et al., 2020).

Another approach is the *a priori* selection of seed regions for subsequent analyses. However, although computationally simpler than mass univariate analyses, this approach is vulnerable to confirmation bias, potentially overlooking other important brain regions (Lv et al., 2018).

Advanced approaches like Multivariate Pattern Analysis have gained traction in addressing these limitations. Unlike traditional univariate methods that analyse single voxel or region-based values, Multivariate Pattern Analysis considers distributed patterns across multiple voxels, offering a more robust means of identifying functional connectivity changes (Weaverdyck et al., 2020).

5.2.1 Aims and Objectives

The primary aim of this chapter was to determine which brain region(s) show evidence of alterations in the brain-wide connectome across AD stages, using a robust machine learning method – Multivariate Pattern Analysis. By identifying key spatial functional connectivity patterns and brain regions contributing significantly to group-level differences, this chapter highlights clinically meaningful targets for potential therapeutic interventions.

A secondary supplementary aim was to address the non-significant findings from Chapter 4 in the CU vs. MCI group comparison by stratifying these groups based on A β status. This stratification aimed to explore whether A β -related subgroup differences could provide further insights.

5.3 Methods

5.3.1 Study Design

As in Chapter 4, ADNI-3 participant data was chosen due to the use of a standardised operating protocol in collecting brain imaging data and the collection of structural and resting-state fMRI data. Relevant to this chapter is the further collection of cortical A β load (via A β -PET) to determine A β status (A β - or A β +).

5.3.2 Study Participants

The same participant sample was used as in Chapter 4: 252 male and female older adults between the ages of 60 and 90. Of the 252, 167 were CU, 68 had evidence of amnesic-MCI, and 17 had DAT. A research diagnosis of CU, MCI, or DAT was determined using a combination of CDR and MMSE (as detailed in Chapter 3.).

5.3.3 Imaging

5.3.3.1 MRI Data Acquisition

See Chapter 3 (Materials and Methods) and Chapter 4 (Whole-Brain Functional Connectivity) for descriptions of the MRI data acquisition parameters used in the ADNI-3 study.

5.3.3.2 MRI Pre-processing and Denoising

For consistency, the same pre-processing and denoising steps were employed for all analyses in this current chapter.

5.3.3.3 PET Data Acquisition

For this chapter, ADNI-3 participants who had received two PET scans, one to measure amyloid aggregation and the other, tau, were selected. Reference to A β status can be found in section 5.5.3.4. ADNI-3 collected evidence of A β accumulation using one of two radiotracers: ^{18}F -Florbetaben or ^{18}F -

Florbetapir. All participants had a 20-minute continuous brain PET scan beginning at either 50 minutes (^{18}F -Florbetapir) or 90 minutes (^{18}F -Florbetaben). ADNI-3 based their PET data acquisition protocol on Lee et al. (2023).

5.3.3.4 Supplementary Analyses: Functional Connectivity Differences Between CU and MCI Stratified By A β -PET Status

Supplementary analyses (beginning at section 5.5.3) involved stratifying CU and MCI groups further to explore whether functional connectivity differences were present between CU and MCI A β subgroups (CU A β - and CU A β +, CU A β - and MCI A β -, CU A β +, and MCI A β +, and MCI A β - and MCI A β +,). This was based on cortical A β load, determined by A β -PET.

University of California, Berkeley determined A β status (A β + / A β -) cut-off thresholds. ADNI-3 data were normalised with whole cerebellum reference region thresholds for the two A β -PET radiotracers. The SUVR values for A β + cut-offs were ≥ 1.08 for ^{18}F -Florbetaben and ≥ 1.11 for ^{18}F -Florbetapir. This was in line with the recommendations of Lee et al. (2023) and Joshi et al. (2012).

A total of 183 out of the main 252 participants were included in supplementary analyses involving CU and MCI participants and stratifying by A β status: CU A β +, (n = 51), CU A β - (n = 81), MCI A β +, (n = 29) and MCI A β - (n = 22).

5.4 Imaging Analysis

5.4.1 Multivariate Pattern Analysis

Multivariate Pattern Analysis allows for measuring network differences at the voxel level (Weaverdyck et al., 2020). CONN computes Multivariate Pattern Analysis functional connectivity maps using PCA. Instead of modelling a seed voxel and analysing each voxel separately, Multivariate Pattern Analysis analyses a set of voxels together, forming a voxel-to-voxel “connectome” (Kazumata et al., 2017). Multivariate Pattern Analysis works by isolating the spatial features of Seed-based connectivity maps (Whitfield-Gabrieli & Nieto-Castañón, 2012). Multivariate Pattern Analysis combines the benefits of pattern analysis techniques and reduced dimensionality (Nieto-Castañón, 2022).

In this study, three group comparisons were used primarily to compare the differences in functional connectivity between earlier vs later AD stages: (1) CU vs MCI, (2) CU vs DAT, and (3) MCI vs DAT.

5.4.2 Whole-Brain Seed-Based Connectivity

Seed-based connectivity analyses were conducted using ROIs derived from group-Multivariate Pattern Analysis. Differences in seed-to-voxel functional connectivity between AD stages were determined by disease stage contrasts (as with Multivariate Pattern Analysis).

Functional connections between Multivariate Pattern Analysis-derived “seeds” and other areas of the brain were extracted because they exhibited differences between groups (CU, MCI, and DAT). The strongest functional connections are reported in-text and shown as images.

5.4.3 Graph Theory

Graph theory measures were used to determine the topological characteristic differences between groups (see Chapter 3 for a full description of each measure).

5.4.4 Supplementary Analyses: CU and MCI A β subgroups

A set of supplementary analyses were conducted to explore sub-group differences between CU and MCI, based on cortical A β status: CU A β - and CU A β +, CU A β - and MCI A β -, CU A β + and MCI A β +, and MCI A β - and MCI A β +. This was based on cortical A β load, determined by A β -PET.

5.4.4.1 Whole-Brain Functional Connectivity: CU and MCI A β subgroups

As with previous analyses outlined in Chapter 4, whole-brain functional connectivity analyses were performed across 164 brain regions (the maximum number of brain regions included in CONN, with the use of the AAL atlas; Rolls et al., 2020), except this time, with the aforementioned four CU and MCI A β sub-groups.

5.4.4.2 Multivariate Pattern Analysis: CU and MCI A β subgroups

Multivariate Pattern Analysis was performed per the last set of analyses, except with the four CU and MCI A β sub-groups.

5.4.4.3 Network-Level Functional Connectivity and Graph Theory: CU and MCI A β subgroups

Network-level functional connectivity analyses were performed “within” and “between” eight resting-state networks: Default Mode, Sensorimotor, Visual, Salience, Dorsal Attention, Frontoparietal, Language, and Cerebellar. Each resting-state network was composed of the following sub-regions:

1. Default Mode: medial prefrontal cortex, left and right lateral parietal cortices, and posterior cingulate cortex.
2. Sensorimotor: left and right lateral portions and superior portions.
3. Visual: medial portion, occipital portion, and left and right lateral portions.
4. Salience: anterior cingulate cortex, left and right anterior insula, left and right rostral prefrontal cortices, left and right supramarginal gyri.
5. Dorsal Attention: left and right frontal eye fields and left and right intraparietal sulci.
6. Fronto-parietal: left and right lateral prefrontal cortices and left and right posterior parietal cortices.
7. Language: left and right inferior frontal gyri and left and right posterior superior temporal gyri.
8. Cerebellar: anterior and posterior portions.

Graph theory was conducted in the same manner as section 5.4.3.

5.5 Results

5.5.1 Demographic and Clinical Characteristics

The results for the 252 ADNI-3 participants remain the same, as described in Chapter 4.

5.5.2 Functional connectivity

Functional connectivity was measured across three group comparisons: (1) CU vs. MCI, (2) CU vs. DAT, and (3) MCI vs. DAT. Figures 5.1 and 5.2. provide illustrations of the significant relationships found during each group comparison and whether there is evidence of increased vs. decreased functional connectivity patterns between groups.

Firstly, no significant differences in functional connectivity were observed between group comparison 1 (CU vs. MCI) participants, so whole-brain seed-based connectivity was not conducted for this group comparison.

Secondly, for group comparison 2 (CU vs. DAT), the largest cluster had the peak MNI coordinates $(x, y, z) = [-06, -08, 00]$ (located in the left thalamus), $k = 15741$. The largest portion of voxels covered 20% of the precuneus (1138 voxels [7%]). The left thalamus and precuneus were extracted as seed regions for seed-based connectivity analyses.

The seed-based connectivity outcomes for group comparison 2 (CU vs. DAT) were as follows:

Left thalamus: three clusters were found to be different between these groups Cluster 1: peak MNI coordinates = $[+56, +02, -35]$ (located in the right inferior temporal gyrus) showed evidence of reduced functional connectivity among DAT participants, compared to CU, and clusters 2 and 3 showed evidence of increased functional connectivity among DAT compared to CU. Cluster 2: peak MNI coordinates = $[+46, +32, +28]$ (located in the right inferior frontal gyrus [pars triangularis]); cluster 3: peak MNI coordinates = $[+52, -12, +30]$ (located in the right postcentral gyrus).

Precuneus: between the precuneus and the rest of the brain, four clusters were found. Cluster 1: peak MNI coordinates = $[+32, -08, +48]$ (located in the right precentral gyrus); cluster 2: peak MNI

coordinates = [-52, -02, +20] (located in the left precentral gyrus); cluster 3: peak MNI coordinates = [-38, -92, +08] (located in the left middle occipital gyrus); cluster 4: peak MNI coordinates = [-29, +10, -16] (located in the left insula). In terms of alterations in functional connectivity between groups, all but the precuneus to the right precentral connection, which was indicative of DAT demonstrating reduced functional connectivity between the precuneus and other brain regions.

In summary, between CU and DAT participants, the left thalamus and precuneus were extracted as seed regions for seed-based connectivity analyses. When the left thalamus was used as a seed, functional connectivity between the left thalamus and the right inferior temporal gyrus was higher among CU participants than DAT. Compared to CU, functional connectivity was higher among DAT between the left thalamus, the right inferior frontal gyrus (triangularis), and the right postcentral. Next, when the precuneus was used as a seed region, functional connectivity between the precuneus and three regions was higher among CU, compared to DAT: left precentral, left middle occipital gyrus, and left insula. Whereas, between the precuneus and right precentral, functional connectivity was higher among DAT, compared to CU.

Thirdly, for group comparison 3 (MCI vs. DAT), we found evidence of altered functional connectivity for this group comparison between sub-regions of the frontal gyri. Cluster 1: peak MNI coordinates = [-07, -26, +02] (located in the left thalamus). As with CU vs. DAT comparisons, the precuneus was the largest contribution to this cluster). For the voxel thresholded cluster, peak MNI coordinates = [+10, +60, +36] (located in the right medial frontal gyrus [superior part]). Therefore, we also added the precuneus as a supplementary seed region for seed-based connectivity.

Cluster 2: peak MNI coordinates = [+10, +60, +36] (located in the right superior frontal gyrus); cluster 3: peak MNI coordinates = [-14, +12, +58] (located in the left superior medial frontal gyrus).

The seed-based connectivity outcomes for these regions are as follows:

Left thalamus: between the left thalamus and the rest of the brain, one cluster was found to be significant: peak MNI coordinates = [-38, -75, -35] (located in the left Crus II).

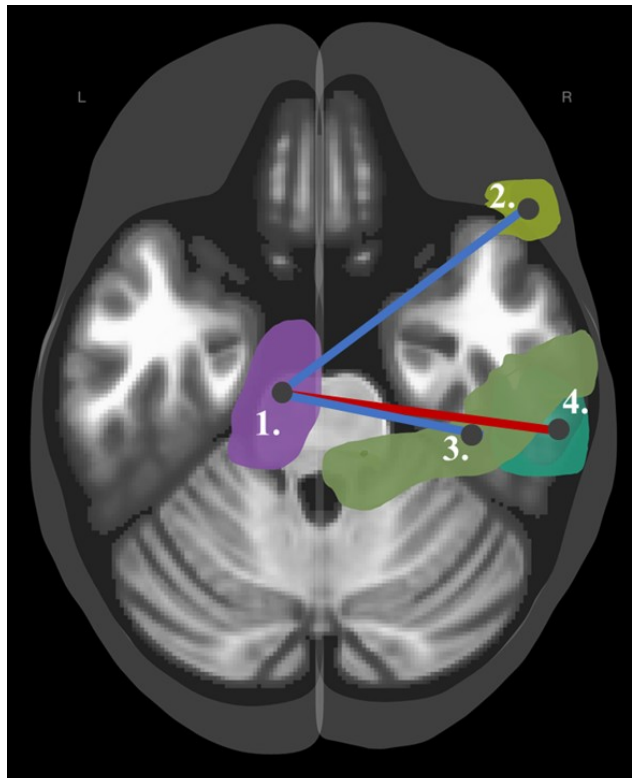
Sub-Regions of the Frontal Gyrus

Right superior frontal gyrus: only one cluster was identified: peak MNI coordinates = [+58, +10, +08] (located in the right Rolandic operculum).

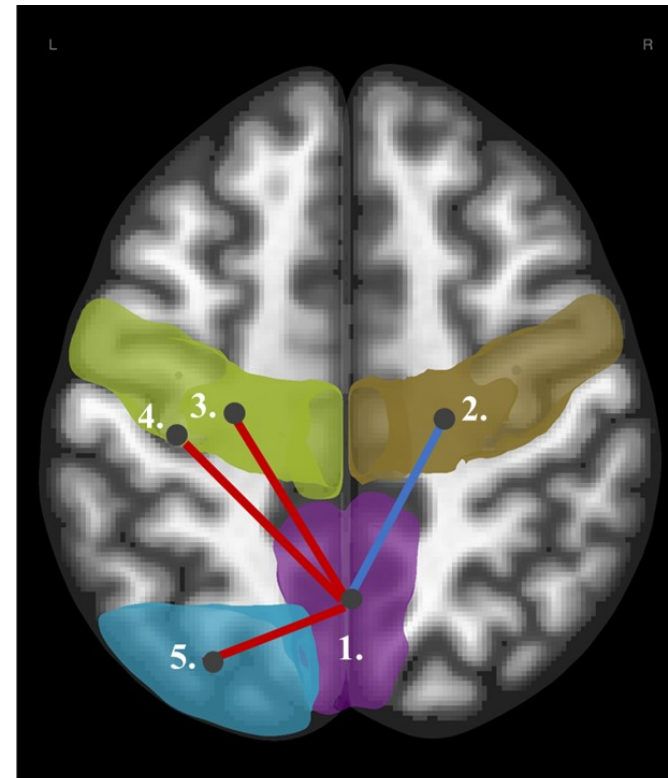
Left superior frontal gyrus: two clusters were found. Cluster 1: peak MNI coordinates = [+44, +38, +18] (located in the right middle frontal gyrus); cluster 2: [-28, +11, -04] (located in the left putamen). Both clusters suggest reduced functional connectivity among DAT participants between the left superior frontal gyrus, the right frontal middle gyrus and the left putamen.

Precuneus: two clusters were found to be significant. Cluster 1: peak MNI co-ordinates = [-50, -10, +50] (located in the left precentral gyrus; cluster 2: peak MNI coordinates = [-42, -12, -06] (located in the left superior temporal gyrus). Between the precuneus and left precentral, there was evidence of increased functional connectivity (among DAT participants) but reduced functional connectivity between the precuneus and left temporal superior gyrus.

In summary, when the left thalamus was used as a seed region, functional connectivity between the left thalamus and left Crus II was higher among DAT than MCI. Next, when the precuneus was used as a seed region, functional connectivity between the precuneus and left superior temporal gyrus was higher among MCI, compared to DAT. However, functional connectivity between the precuneus and left precentral was higher among DAT than MCI. The superior frontal gyrus was parcellated into its left and right hemispheric regions. When the right superior frontal gyrus was used as a seed, functional connectivity between the right superior frontal gyrus and right Rolandic operculum was higher among MCI, compared to DAT. When the left superior frontal gyrus was used as a seed region, functional connectivity between the left superior frontal gyrus and left putamen was higher among MCI, compared to DAT.



Left Thalamus



Precuneus

Figure 5.1. Schematic showing statistically significant differences in functional connections between CU and DAT: A combinational approach of Multivariate Pattern Analysis and seed-based connectivity analysis

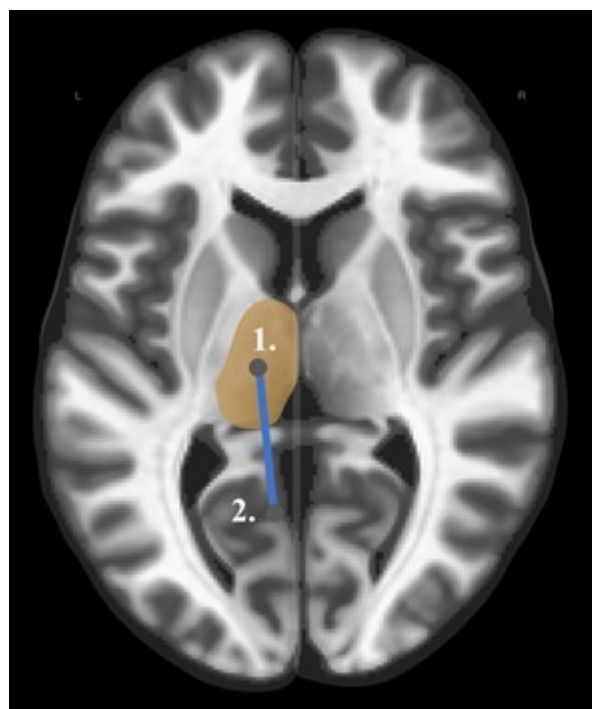
Note:

This figure aims to provide a visual representation of functional connectivity patterns between cognitively unimpaired (CU) and dementia due to Alzheimer's disease (DAT) participants.

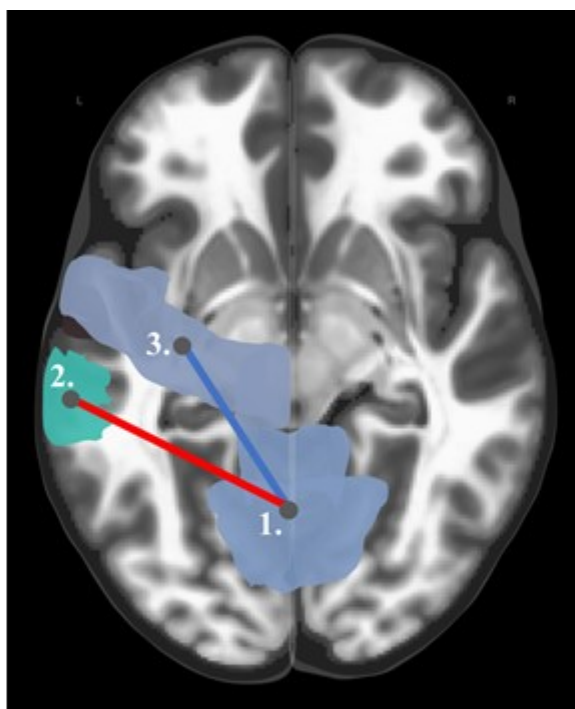
Red indicates that functional connectivity is higher among CU (cognitively unimpaired) compared to DAT (dementia due to Alzheimer's disease); blue indicates that functional connectivity is higher among DAT compared to CU.

Left: the left thalamus (derived from Multivariate Pattern Analysis) was used as a seed region for seed-based connectivity analysis. 1 = left thalamus; 2 = right inferior frontal gyrus (pars triangularis); 3 = right postcentral ; 4 = right inferior temporal gyrus.

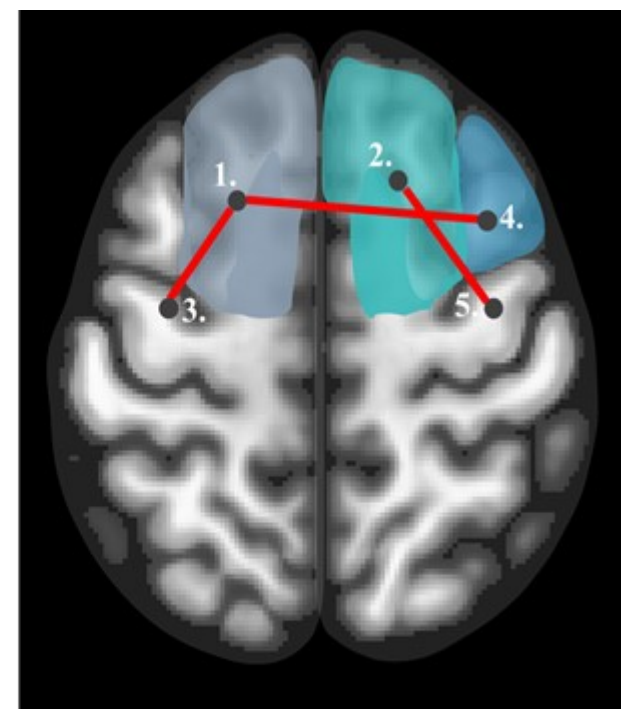
Right: the precuneus (derived from Multivariate Pattern Analysis) was used as a seed region for seed-based connectivity analysis. 1 = precuneus; 2 = right precentral; 3= left precentral; 4 = left insula; 5 = left middle occipital gyrus.



Left Thalamus



Precuneus



Left and Right Superior Frontal Gyrus

Figure 5.2. Schematic showing statistically significant differences in functional connections between MCI and DAT: A combinational approach of Multivariate Pattern Analysis and seed-based connectivity analysis

Note:

The aim of this figure is to provide a visual representation of functional connectivity patterns between mild cognitive impairment (MCI) and dementia due to Alzheimer's disease (DAT) participants.

Red indicates that functional connectivity is higher among MCI (mild cognitive impairment) than among DAT (dementia due to Alzheimer's disease); blue indicates that functional connectivity is higher among DAT than among MCI.

Left: the left thalamus (derived from Multivariate Pattern Analysis) was used as a seed region for seed-based connectivity analysis. 1 = left thalamus; 2 = left Crus II.

Middle: the precuneus (derived from Multivariate Pattern Analysis) was used as a seed region for seed-based connectivity analysis. 1 = precuneus; 2 = left superior temporal gyrus; 3 = left precentral gyrus.

Right: the left and right portions of the superior frontal gyrus (derived from Multivariate Pattern Analysis) were used as a seed region for seed-based connectivity analysis. 1 = left superior frontal gyrus; 2 = right superior frontal gyrus; 3 = left putamen; 4 = right middle frontal gyrus; 5 = right Rolandic operculum.

5.5.3 Supplementary Analyses and Results: CU and MCI A β subgroups

To explore the possible reasons underlying the non-significant findings between CU and MCI further, analyses were emulated between CU and MCI sub-groups when stratified by A β status (CU A β -, CU A β +, MCI A β -, and MCI A β +) . The analyses included whole-brain ROI-to-ROI (Chapter 4) and Multivariate Pattern Analysis (current Chapter / Chapter 5). A summary of the results derived from supplementary analyses can be found in Table 5.1.

5.5.3.1 Whole-Brain ROI-to-ROI Functional Connectivity Between CU and MCI A β Subgroups

No significant differences were observed between all four CU and MCI A β - and A β + sub-group comparisons ($p > .05$).

5.5.3.2 Multivariate Pattern Analysis Between CU and MCI A β Subgroups

Differences in functional connectivity were observed between all CU and MCI A β status sub-groups, bar CU A β - vs. CU A β +. All functional connectivity directions suggested that Group 1 functional connectivity was higher than Group 2, e.g., for CU A β + vs MCI A β +, functional connectivity was higher among CU A β + participants compared to MCI A β +. However, the peak FWE were $p > .05$ for all clusters and group comparisons. As a result, no Multivariate Pattern Analysis “seed” regions were considered for further analyses (seed-based connectivity).

5.5.3.2.1 CU A β + vs. MCI A β +

Five clusters were found when investigating differences in functional connectivity between CU and MCI A β + participants.

Cluster 1 of 5 peak MNI coordinates = [+10, +12, +52] (located in the right supplementary motor area); cluster 2 of 5 peak MNI coordinates = [-18, -62, +18] (located in the left calcarine); cluster 3 of 5 peak MNI coordinates = [-04, +28, +28] (located in the left anterior cingulum); and cluster 4 of 5 peak MNI

coordinates = [+12, +14, +52] (located in the right supplementary motor area); and cluster 5 of 5 peak MNI coordinates = [-16, -56, +18] (located in the left precuneus).

5.5.3.2.2 CU A β - vs. MCI A β -

One cluster was found when investigating differences in functional connectivity between CU and MCI A β - participants. However, the peak FWE were $p > .05$. Cluster 1 of 1 peak MNI coordinates = [-16, -56, +18] (located in the left precuneus).

5.5.3.2.3 CU A β - vs. CU A β +

No significant differences were observed between CU- and CU+ A β sub-groups.

5.5.3.2.4 MCI A β - vs. MCI A β +

One cluster was found when investigating differences in functional connectivity between MCI A β - and A β + participants.

However, the peak FWE were $p > .05$. Cluster 1 of 1 peak MNI coordinates = [+04, +08, +74] (located in the right supplementary motor area).

5.5.3.3 Section Summary

No significant differences in functional connectivity patterns were found for the four group comparisons with whole-brain ROI-to-ROI (Chapter 4) and Multivariate Pattern Analysis (current chapter / Chapter 5). Therefore, network-level analyses were run to determine whether early-stage differences, whilst stratifying further by A β status, would uncover differences in functional connectivity between sub-regions of various resting-state networks.

5.5.3.4 Network-Level Functional Connectivity Between CU and MCI A β Subgroups

Differences in functional connectivity across four groups were investigated at the network level via the extraction of eight resting-state networks (Default Mode, Sensorimotor, Dorsal Attention,

Frontoparietal, Salience, Visual, Language, and Cerebellar networks). Functional connectivity was measured (a) “within” each of the eight resting-state networks separately and (b) “between” all eight resting-state networks. FDR and FWE correction significance was set at $p < .05$.

5.5.3.4.1 CU A β + vs. MCI A β +

When comparing functional connectivity between CU A β + vs MCI A β + participants within resting-state networks, a single ROI-to-ROI functional connection was found to be significantly different between both sub-groups: Salience network, left anterior insula [-44, +13, +01] – Salience network, left rostral prefrontal cortex [-32, +45, +27], $T(182) = -2.83$, uncorrected $p = .005$, FDR $p = .031$. This suggests increased functional connectivity among MCI A β + relative to CU A β +

Next, functional connectivity was compared between these sub-groups of all eight resting-state networks. One significantly different functional connection survived FDR p correction: Default Mode network, medial prefrontal cortex [+01, +55, -03] – Language network, left posterior superior temporal gyrus [-57, -47, +15], $T(75) = 3.52$, uncorrected $p < .001$, FDR $p = .023$. This suggests increased functional connectivity among CU A β + relative to MCI A β +

5.5.3.4.2 CU A β - vs. MCI A β -

Functional connectivity analysis was repeated for CU- vs. MCI- participants within resting-state networks. More functional connectivity differences were present within the Visual, Dorsal Attention, and Cerebellar networks. In total, four differences in functional connectivity were found – all of which were suggestive of increased functional connectivity among CU A β -, relative to MCI A β -: (1) Visual network, right lateral portion [+38 -72 +13] – Visual network, left lateral portion [-37, -79, +10], $T(192) = 3.33$, uncorrected $p = .001$, FDR $p = .001$; (2) Visual network, occipital portion [00, -93, -04] – Visual network, medial portion [+02, -79, +12], $T(192) = 3.32$, uncorrected $p = .001$, FDR $p = .003$; (3) Dorsal Attention, right inferior parietal sulcus [+39, -42, +54] – Dorsal Attention, left inferior parietal sulcus [-39, -43, +52], $T(192) = 2.50$, uncorrected $p = .013$, FDR $p = .040$, and (4) Cerebellar, anterior portion

[00, -63, -30] – Cerebellar, posterior portion [00, -79, -32], $T(192) = 3.25$, uncorrected $p = .001$, FDR $p = .001$.

Next, functional connectivity was compared between these sub-groups of all eight resting-state networks. One cluster was found to be statistically significant, and suggestive of higher functional connectivity among CU A β -, compared to MCI A β -. (1) Visual network, medial portion [+02, -79, +12] – Default mode, posterior cingulate cortex [+01, -61, +38], $T(192) = 3.56$, uncorrected $p < .001$, FDR $p = .014$.

5.5.3.4.3 CU A β - vs. CU A β +

Between CU A β - and CU A β + participants, no clusters survived p -FDR, both within- and between-resting-state networks.

5.5.3.4.4 MCI A β - vs. MCI A β +

When measuring functional connectivity within-resting-state networks, one functional connection demonstrated significant differences between MCI A β - vs. MCI A β +: (1) Sensorimotor network, left lateral portion [-55, -12, +29] – Sensorimotor network, superior portion [00, -31, +67], $T(49) = 2.34$, uncorrected $p = .023$, FDR $p = .047$. Functional connectivity was higher among MCI A β - participants than MCI A β +. However, no significant results were found between resting-state networks when comparing functional connectivity between MCI A β - and MCI A β + sub-groups.

Table 5.1. Sub-Group Analysis by A β Status for CU and MCI Participants at Whole-Brain- and Network-Level

		Whole-Brain-Level ¹		Network-Level ¹				
Group Comparison		ROI - to -ROI	Multivariate Pattern Analysis	“Within” Resting State Networks			“Between” Resting State Networks	
<i>Between Groups</i>	<i>CU+ vs. MCI+</i>	×	×	✓	Salience		✓	Default Mode – to – Language
	<i>CU- vs. MCI-</i>	×	×	✓✓✓	Visual	Dorsal Attention	Cerebellar	✓ Visual-to-Default Mode
<i>Within Groups</i>	<i>CU- vs. CU+</i>	×	×	×			×	
	<i>MCI- vs. MCI+</i>	×	×	✓	Sensorimotor		×	

Notes. CU = cognitively unimpaired; MCI = mild cognitive impairment; + / - = amyloid-beta positive/negative status; × = no significant result(s) for this analysis and sub-group analysis; ✓ = significant results for this analysis and sub-group analysis. ¹Evidence of significant results (× / ✓) was included in-text based on surviving false discovery rate (FDR)-correction and family-wise error (FWE) with significance set at $p < .05$.

5.5.3.5 Network-Level Graph Theory Between CU and MCI A β Subgroups

Across all four group comparisons, only average path length revealed differences between CU and MCI participants, suggesting that the optimal path differs between most group comparisons. Average path length is an alternative measure of node centrality (*“Graph Measures [ROI-level]”*, CONN, n, d).

5.5.3.5.1 CU A β + vs. MCI A β +

Four subregions of four resting-state networks (Default Mode, Dorsal Attention, Frontoparietal, and Visual) significantly differed between CU A β + and MCI A β + participants. Three clusters suggested lower node centrality among CU A β + compared to MCI A β + (increased functional connectivity among MCI+): (1) Default Mode, posterior cingulate cortex [+01, -61, +38], $T(87) = -2.53$, uncorrected $p = .013$, FDR $p = .039$; (2) Dorsal Attention, left inferior parietal sulcus [-39, -43, +52], $T(140) = -2.32$, uncorrected $p = .022$, FDR $p = .043$; (3) Frontoparietal, left lateral prefrontal cortex [-43, +33, +28], $T(95) = -6.56$, uncorrected $p < .001$, FDR $p < .001$; Frontoparietal, right lateral prefrontal cortex [+41, +38, +30], $T(80) = -3.35$, uncorrected $p < .001$, FDR $p < .001$.

One cluster suggested higher node centrality among CU A β + (decreased functional connectivity among MCI A β +)ate: Visual, right lateral portion [+38, -72, +13], $T(103) = 4.96$, uncorrected $p < .001$, FDR $p < .001$.

5.5.3.5.2 CU A β - vs. MCI A β -

The highest frequency of altered average path lengths was found between CU A β - and MCI A β - participants across six out of eight resting-state networks: Default Mode, Sensorimotor, Visual, Dorsal Attention, Frontoparietal, and Language. Importantly, all results regarding average path length for this group contrast suggested that average path length is higher among all the following regions among MCI A β - participants.

- Default Mode, posterior cingulate cortex [+01, -61, +38], $T(91) = -5.68$, uncorrected $p < .001$, FDR $p < .001$; Default Mode, medial prefrontal cortex [+01, +55, -03], $T(28) = -4.49$, uncorrected $p < .001$, FDR $p < .001$.

- Sensorimotor, left lateral portion [-55, -12, +29], $T(95) = 5.88$, uncorrected $p < .001$, FDR $p < .001$; Sensorimotor, superior portion [00, -31, +67], $T(32) = -3.36$, uncorrected $p < .001$, FDR $p = .002$.
- Visual, medial portion [+02, -79, +12], $T(56) = 7.16$, uncorrected $p < .001$, FDR $p < .001$; Visual, left lateral portion [-37, -79, +10], $T(121) = -4.51$, uncorrected $p < .001$, FDR $p < .001$.
- Dorsal Attention, left frontal eye fields [-27, -09, +64], $T(56) = -7.02$, uncorrected $p < .001$, FDR $p < .001$; Dorsal Attention, left inferior parietal sulcus [-39, -43, +52], $T(136) = -5.79$, uncorrected $p < .001$, FDR $p < .001$; Dorsal Attention, right inferior parietal sulcus [+39, -42, +54], $T(125) = 5.12$, uncorrected $p < .001$, FDR $p < .001$.
- Frontoparietal, left lateral prefrontal cortex [-43, +33, +28], $T(87) = 8.89$, uncorrected $p < .001$, FDR $p < .001$; Frontoparietal, right lateral prefrontal cortex [+41, +38, +30], $T(83) = -3.74$, uncorrected $p < .001$, FDR $p < .001$; Frontoparietal, left posterior parietal cortex [+52, -52, +45], $T(103) = -2.85$, uncorrected $p = .005$, FDR $p = .007$.
- Language, left inferior frontal gyrus [-51, +26, +02], $T(92) = -5.60$, uncorrected $p < .001$, FDR $p < .001$; Language, left posterior superior temporal gyrus [-57, -47, +15], $T(89) = -5.48$, uncorrected $p < .001$, FDR $p < .001$; Language, right posterior superior temporal gyrus [59, -42, +13], $T(89) = -3.13$, uncorrected $p = .002$, FDR $p = .003$.

5.5.3.5.3 CU A β - and CU A β +

Node centrality was found among CU- compared to CU+ across two resting-state networks and three brain regions: Default Mode, posterior cingulate cortex [+01, -61, +38], $T(58) = 7.29$, uncorrected $p < .001$, FDR $p < .001$; Default Mode, left lateral parietal cortex [-39, -77, +33], $T(81) = 6.99$, uncorrected $p < .001$, FDR $p < .001$; and Dorsal Attention, right intraparietal sulcus [+39, -42, +54], $T(89) = 3.79$, uncorrected $p < .001$, FDR $p < .001$.

5.5.3.5.4 MCI A β - and MCI A β +

Higher node centrality (and decreased functional connectivity) was found among MCI A β - participants for Sensorimotor, left lateral portion [-55, -12, +29], $T(24) = 4.21$, uncorrected $p < .001$, FDR $p < .001$; but lower node centrality (and increased functional connectivity) for MCI A β - participants for Visual, left lateral portion [-37, -79, +10], $T(34) = -7.24$, uncorrected $p < .001$, FDR $p < .001$.

5.6 Discussion

Traditional whole-brain functional connectivity analyses, such as ROI-to-ROI approaches, often yield many altered functional connections when comparing subject groups. This abundance may prove challenging to interpret. To address this, we adopted whole-brain Multivariate Pattern Analysis, which enables the identification of a small, focused set of ROIs that may explain the most variance between groups.

Our analyses identified the left thalamus and precuneus as key ROIs for two out of three group comparisons: CU vs. DAT and MCI vs. DAT. Whilst subdivisions of the frontal gyri were Multivariate Pattern Analysis-derived seed regions unique to MCI vs. DAT group analyses only. These findings suggest that the left thalamus, precuneus, and frontal gyri play potentially critical roles in AD progression.

5.6.1 Key Brain Regions Demonstrating Group-Level Differences in Functional Connectivity Via Multivariate Pattern Analysis

5.6.1.1 Thalamus

The left thalamus emerged as a significant seed region in the comparison of CU vs. DAT (peak MNI coordinates = -06, -08, 00) and MCI vs. DAT (peak MNI coordinates = -07, -26, +02) group. This multifunctional structure has been called the “gateway of consciousness” (Crick & Koch, 2003). The thalamus supports a wide range of functions, including somatosensory (Klostermann et al., 2009) and sensory (Wolff et al., 2021 [review]) processing, as well as its involvement in cognition (Saalmann & Kastner, 2015), language (Hebb & Ojemann, 2013), consciousness (experiencing one’s environment and internal state; Redinbaugh et al., 2020), and as the bridge between perception and cognition (Wolff et al., 2021 [review]).

Regions comprising the sensorimotor have shown functional connectivity with the thalamus (Kawabata et al., 2021), a key ROI extracted via Multivariate Pattern Analysis in this current study. This reinforces that sensory areas – such as the thalamus – are potentially implicated in AD on a

functional scale. Furthermore, there appears to be a bidirectional relationship between changes to the visual system and brain regions associated with sensory processing. For example, in a systematic review and meta-analysis by Cao et al. (2023), visual impairment was found to be a potential risk factor for future cognitive impairment and dementia via a large-scale meta-analysis comprising data from > 75,000 participants (Cao et al., 2023). The exact mechanisms underlying the links between visual and hearing impairment and cognitive impairment are unclear. For hearing loss, Tarawneh et al. highlighted the “sensory deprivation theory” in their 2022 review. The “sensory deprivation theory” suggests that sensory degradation in those with hearing impairment may be attributed to loss of input to the cortex, resulting in functional and structural deficits within auditory and cognitive systems (Tarawneh et al., 2022), and shrinkage of the optic tract was also found among patients with thalamic stroke (Ye et al., 2022).

Therefore, understanding the intricate functional connectivity patterns involving the thalamus and other brain regions is crucial, as these alterations may underpin sensory and cognitive deficits observed in AD, potentially offering targets for early intervention and therapeutic strategies.

5.6.1.2 Precuneus

As with the left thalamus, the precuneus was extracted as a seed region for CU vs. DAT and MCI vs. DAT group comparisons. The precuneus is a well-researched brain area because it is a connectivity hub within large-scale brain networks (e.g., Aghakhanyan et al., 2018). As with the thalamus, the precuneus supports multiple functional processes, such as one’s sense of self, consciousness, visuospatial processing, executive function, and memory; according to a review by Cavanna and Trimble (2006). Sensory processing via connections to high-order cortices involves sensory processing of visual, auditory, and somatosensory information (Al-Ramadhani et al., 2021), with some studies finding the precuneus to be functionally connected to the medial thalamus (e.g., Kawabata et al., 2021). The precuneus is a site of high metabolic demand, with a glucose consumption rate ~35% higher than other areas of the cerebral cortex (as described in a review by Gusnard & Raichle, 2001). Gouras (2016) found that the precuneus exhibited hypermetabolism at early preclinical AD stages of A β deposition.

They hypothesised that hyperactivity induced by A β accumulation may create a state of heightened vulnerability for future neurodegeneration.

Understanding the role of the precuneus and its functional connectivity with other brain regions, especially in how functional connectivity changes within and between this region across AD stages, to understand better what happens over the course of disease progression.

5.6.1.3 Frontal Gyri

Unlike the left thalamus and precuneus, the superior frontal gyri (left and right portions [peak MNI coordinates = -14, +12, +58 and +10, +60, +36 respectively) were extracted as seed regions specifically when comparing MCI and DAT participants only.

Research into this area is limited, but a study by Tang et al. (2021) found that functional connectivity between the left superior frontal gyrus and right Crus II was positively correlated with digit span test scores (a measure of verbal memory) among MCI participants (Tang et al., 2021). This suggests disruptions in functional connectivity within cognitively relevant brain regions among MCI, and these functional changes may represent compensation and are associated with cognitive function (Tang et al., 2021). Furthermore, compared with the subjective cognitive decline group, the early-MCI group showed decreased functional connectivity in the right superior frontal gyrus. In contrast, the late-MCI group showed decreased functional connectivity in the left middle temporal gyrus (Xu et al., 2021).

5.6.2 Functionally Connected Brain Regions Via Seed-Based Connectivity Analysis

5.6.2.1 Thalamus as a Seed Region

5.6.2.1.1 Inferior Frontal Gyrus

Hampshire et al. (2010) demonstrated that the right inferior frontal gyrus is actively recruited during task-based fMRI paradigms when participants detect important cues. In the context of AD research, Eliasova et al. (2014) conducted a pilot study using repetitive transcranial magnetic stimulation to target this region in a small sample of older adults ($n = 10$) with MCI or “mild dementia.” The study observed

statistically significant improvements in attention and motor speed following the intervention, suggesting potential benefits of modulating cortical activity in this area.

Despite these promising findings, research directly targeting the right inferior frontal gyrus within AD and dementia studies remains limited. Moreover, investigations into specific subregions, such as the pars triangularis, are even scarcer, underscoring a gap in the literature that warrants further exploration.

5.6.2.1.2 Inferior Temporal Gyrus

Xiong et al. (2020) reported decreases in regional homogeneity within the inferior temporal gyrus among MCI participants with type 2 diabetes compared to normal controls with type 2 diabetes. Additionally, this group exhibited altered nodal characteristics, including betweenness centrality, degree, and efficiency.

The researchers proposed that decreased neural coherence in the inferior temporal gyrus may significantly impact cognitive performance. Given the region's role in visual processing, complex object feature representation, and word and number recognition, disruptions in its function could contribute to poorer outcomes in cognitive testing (Xiong et al., 2020).

5.6.2.1.3 Postcentral Gyrus

In "*Neuroanatomy, Postcentral Gyrus*", the postcentral gyrus houses the primary somatosensory cortex, a region essential in proprioception (the body's ability to sense its position and movement; DiGuseppi & Tadi, 2023). In the context of AD, a study investigating N6-methyladenosine ribonucleic acid methylation (an epigenetic modification associated with neurobiological processes involved in ageing; Liu et al., 2023) found notable changes in this region. Specifically, the writer protein RBM15 was downregulated with AD compared to controls (Liu et al., 2023).

5.6.2.1.4 Crus II

In this chapter, analyses revealed that, between MCI and DAT participants, the left thalamus exhibited group-level functional connectivity differences with the left Crus II of the cerebellum only.

Each human cerebellar hemisphere is parcellated into several lobes, lobules, and zones, with the Crus II being one of its sub-regions (Schmahmann et al., 1999).

One study by Tang et al. (2021) found that functional connectivity changes between the left Crus II and the right thalamus were associated with cognitive decline in AD. The same functional connection was associated with attention deficit among participants with MCI. Notably, this connection was associated with attention deficits in participants with MCI, although the study identified the opposite hemisphere compared to the findings presented in this chapter.

5.6.2.2 Precuneus as a Seed Region

5.6.2.2.1 Precentral Gyrus

This region has been implicated in anosognosia, the condition in which individuals are unaware of their own cognitive deficits or the severity of bodily impairments, though this has primarily been studied in terms of volumetric rather than functional measurements (Valera-Bermejo et al., 2020). Specifically, non-memory anosognosia was associated with episodic and semantic memory and precentral gyrus volume (Valera-Bermejo et al., 2020). Furthermore, in a study comprised of those with either posterior cortical atrophy or semantic dementia, those with the former were observed to demonstrate decreased functional connectivity between the left precentral gyrus and left primary visual cortex (V1; Chen et al., 2022). These regions are crucial for controlling eye movement and visual attention (Chen et al., 2022).

5.6.2.2.2 Middle Occipital Gyrus

Regarding the precuneus, which in this chapter, showed group-level differences in functional connectivity between CU and AD participants, Huang et al. (2024) found that using a brain-wide functional connectivity approach, the connectivity between the right middle occipital gyrus and the left

angular gyrus was positively correlated with episodic memory in older adults with subjective cognitive decline. This suggests a potential link between these regions and memory processes in the early stages of cognitive decline (Huang et al., 2024).

5.6.2.2.3 Insula

The human insula plays a role in a variety of functions, including both sensory and affective processing and cognitive function (Uddin et al., 2017). In the context of AD research, a study on individuals with subjective cognitive decline found that different insula sub-regions exhibited varying functional connectivity patterns. These patterns were associated with distinct functional brain networks, including the executive control, salience, and sensorimotor networks. These were, in turn, impacted differently in participants with subjective cognitive decline compared to healthy controls (Tian et al., 2024). These functional connectivity patterns were also associated with cognitive performance among those with subjective cognitive decline (Tian et al., 2024).

5.6.2.3 Left and Right Superior Frontal Gyri as Seed Regions

5.6.2.3.1 Rolandic Operculum

The right Rolandic operculum involves various functions, including emotional and sensory processing (Triarhou, 2021). Although not directly a measure of functional connectivity, group differences in neural activity (as measured by dynamic ALFF) showed differences between amnestic- vs non-amnestic-MCI (Zhong et al., 2022). Furthermore, one study found an interaction effect of the *APOE* $\epsilon 2$ allele on functional connectivity between the right Ch4 / nucleus basalis of Meynert and the left Rolandic operculum among MCI participants (Liu et al., 2022).

5.6.2.3.2 Middle Frontal Gyrus

The right middle frontal gyrus may serve as a key nodal connection linking the ventral and dorsal networks, functioning as a “circuit-breaker” that helps to reorientate the individual’s attention to novel stimuli (Corbetta et al., 2008). Li et al. (2021) found that MCI exhibited significantly lower clustering

coefficients in the left middle frontal gyrus than normal controls. This suggests potential disruptions in network organisation within this region among those with MCI (Li et al., 2021).

5.6.2.3.3 Putamen

The putamen, located in the basal ganglia, plays a significant role in reinforcement learning, motor skills, and language processing (Viñas-Guasch & Wu, 2017). In AD, research has shown that the putamen exhibits reduced functional connectivity with the nucleus basalis of Meynert in AD participants (Yan et al., 2020). This suggests that the communication between the putamen and the nucleus basalis of Meynert, which is crucial for cholinergic pathways, is impaired in AD. Such reductions in functional connectivity may reflect the cholinergic dysfunction commonly associated with AD pathology (Yan et al., 2020).

5.6.3 Network-Level Functional Connectivity Differences Between CU and MCI A β ⁺ and A β ⁻ Participants

When comparing functional connectivity between CU and MCI A β ⁺ and A β ⁻ participants, differences were only observed at the resting-state network level. Specifically, most group-level differences were seen between CU⁻ vs MCI⁻ participants (15 differences), followed by CU⁺ vs MCI⁺ (five differences), CU⁻ vs CU⁺ (three differences), and MCI⁻ vs MCI⁺ (two differences).

The Default Mode, Dorsal Attention, and Frontoparietal were affected most frequently (five times) compared to other resting-state networks: Visual (four times), Sensorimotor (three times), Language (three times), and Cerebellar (none).

These findings are unexpected, as they appear to suggest that more evidence of network-level disruption exists among those with lower levels of A β deposition. For example, the Default Mode network, in particular, is vulnerable to A β -related disruptions, as it supports memory and self-referential thought (Palmqvist et al., 2017).

The greater disruptions in network-level functional connectivity observed in CU⁻ and MCI⁻ participants compared to CU⁺ and MCI⁺ groups could be explained by several factors. One possibility is that in

A β ⁺ individuals (CU⁺ and MCI⁺), the brain may initially engage compensatory mechanisms, such as increased functional connectivity within certain networks. This could mask the early effects of A β deposition and result in fewer observable differences at the group level in A β ⁺ individuals.

In contrast, A β ⁻ participants (CU⁻ and MCI⁻) may represent a more heterogeneous group regarding underlying pathology, with non-A β factors - such as tauopathy, vascular changes, or other neurodegenerative conditions - driving cognitive decline. These alternative pathologies could cause more widespread functional connectivity disruptions across multiple networks, potentially accounting for the observed differences between CU⁻ and MCI⁻ groups in this chapter.

5.6.4 Patterns of Increased and Decreased Functional Connectivity Between Groups

An important consideration is that altered functional connectivity between groups was found in both ‘directions’: increased and decreased functional connectivity at the AD stage (relative to CU and MCI). These opposing functional connectivity patterns may reflect distinct neuro-mechanisms at the neuronal levels.

One hypothesis in AD research suggests an imbalance in this excitation and inhibition, resulting in increased functional connectivity, that may contribute to cognitive decline seen in those with AD. This is due to the hypersynchrony seen among groups of neurons, as found by magnetoencephalography (Ramírez-Toraño et al., 2021). Pusil et al. (2019) proposed a progression model from MCI to AD - termed the “X” model. To which “hyper-synchronisation” (oscillatory activity) may precede the conversion from MCI to AD – and therefore suggesting its role for dementia development due to “network breakdown” at later AD stages (Pusil et al., 2019).

On the other hand, reduced functional connectivity observed across the AD continuum may be driven by different neuro-mechanisms. Zhao et al. (2022) found that reduced dynamic functional connectivity (changes to functional connectivity over brief periods) was lower in both MCI and AD patients, with disease severity correlating with decreased dynamic functional connectivity in the frontal and temporal cortices. This reduction was associated with lower cognitive performance, leading the researchers to

propose that dynamic functional connectivity, particularly in the temporal lobe, could be a potential biomarker for future AD studies (Zhao et al., 2022).

The lack of significant results between CU and MCI participants could be attributed to several factors. First, it may suggest that Multivariate Pattern Analysis was not sensitive enough to detect differences between these groups or that insufficient statistical power (i.e., too small sample sizes between CU and MCI) prevented the detection of subtle differences in functional connectivity. Additionally, the heterogeneity within the sub-groups could have diluted the results. For example, the MCI group may include participants with a range of cognitive decline severity, from those showing subtle cognitive changes to those whose deficits are closer to the AD stage.

5.7 Conclusions and Next Steps

This chapter aimed to employ a data-driven approach to identify and extract key ROIs that exhibited the most variance between AD stages by utilising a combined approach of whole-brain Multivariate Pattern Analysis and seed-based connectivity. The results highlight the thalamus, precuneus, and sub-regions of the frontal gyri as regions that demonstrate significant differences in functional connectivity between various other areas, exhibiting increased or decreased patterns relative to another group.

The next chapter will build on these findings by extracting these functional connections and exploring their relationships with AD biomarkers ($A\beta$ and tau) and multidomain cognitive performance.

Chapter 6: AD Biomarkers as Moderators of the Relationships Between Functional Connectivity and Multidomain Cognitive Performance

6.1 Abstract

Background and Purpose: This Chapter investigated the differential roles of A β and tau in moderating the relationship between functional connectivity and multidomain cognitive performance in older adults, using data from the ADNI-3 cohort.

Methods: A cross-sectional analysis was conducted on 185 older adults newly enrolled in the ADNI-3 study, categorised as CU ($n = 124$), MCI ($n = 49$), or DAT ($n = 12$). Regional A β and tau SUVR were extracted for each participant, alongside scores from the NEUROBAT cognitive battery.

Results: Tau moderated more relationships between functional connectivity and multidomain cognitive performance than A β . These effects were more pronounced in MCI participants compared to CU. Both A β and tau were more linked to moderating functional connectivity's impact on visuospatial processing. No significant relationships were present among DAT participants. Importantly, none of the identified relationships survived correction for multiple comparisons.

Conclusions: Regional tau appears to play a stronger role than A β in moderating the association between functional connectivity and multidomain cognitive performance, particularly in MCI. Nevertheless, these findings require validation because the results were no longer significant when correcting for the number of hypotheses tested.

6.2 Background

6.2.1 Functional Connectivity and Cognition

Functional connectivity plays an important role in supporting cognitive performance. Research has demonstrated that task engagement increases activity within “task-positive networks”, emphasising the intrinsic link between functional connectivity and mental processes (Fox et al., 2005).

Ageing is associated with reduced functional connectivity, often in parallel with reductions in cognitive performance. For instance, longitudinal changes in functional connectivity strength in the left precuneus were associated with an ageing-related decline in global cognition among cognitively unimpaired older adults (Li et al., 2020). The authors proposed that changes in functional connectivity strength within the precuneus may underlie a decline in global cognition during normal ageing (Li et al., 2020).

Over AD, those with MCI often exhibit increased functional connectivity. This is hypothesised to act as a compensatory mechanism to sustain cognitive performance (e.g., Qiu et al., 2022).

Further evidence supporting the relationship between functional connectivity and cognition stems from a study by Behfar et al. (2023). In their research, participants with AD dementia underwent eight to 12 weeks of cognitive stimulation therapy. Post-intervention, these participants improved mental performance and reduced behavioural and psychological symptoms compared to baseline scores (Behfar et al., 2023). Furthermore, the authors identified these relationships as further associated with the up-regulation of functional connectivity between the left posterior hippocampus and left postcentral gyrus (Behfar et al., 2023). This suggests that cognitive stimulation may induce short-term improvements in mental performance and support the idea of “complementary neuroplasticity mechanisms” within the brain that may improve cognitive dysfunction and quality of life in this clinical group (Behfar et al., 2023).

6.2.2 AD Biomarkers and Cognition

The temporal relationship between A β , tau, and cognitive decline in AD typically begins with early A β deposition in the brain, often decades before the onset of clinical symptoms (Jagust et al., 2023). On

the other hand, tau pathology initially forms in the entorhinal cortex and hippocampus and spreads to the neocortex (Braak & Braak, 1991). According to the AT[N] criteria (Jack et al., 2016), A β and tau biomarkers are more predictive of early dementia status. In contrast, markers of neurodegeneration, such as glucose hypometabolism, are more indicative of advanced dementia stages (Hammond et al., 2020).

Both the presence of A β and tau are linked to cognitive decline among older adults. For instance, a combination of abnormally elevated A β - and tau-PET levels was strongly associated with short-term cognitive decline within three to five years among cognitively unimpaired older adults. Additionally, one longitudinal study found that, over seven years and among CU older adults, A β changes were associated with tau changes, but tau was more closely related to cognitive decline (Hanseeuw et al., 2019).

6.2.3 Aims and Objectives

Building on the established relationships between (a) functional connectivity and cognition and (b) AD biomarkers and cognition, this Chapter sought to explore these relationships further. Specifically, we hypothesised that regional or localised burden of A β and tau – at sites where functional connectivity was significantly altered across AD stages – would moderate the relationships between functional connectivity and multidomain cognitive performance. Functional connections were identified using a data-driven, hypothesis-free, Multivariate Pattern Analysis to determine seed regions, followed by seed-based connectivity analysis, as detailed in Chapter 5.

We predicted that tau would moderate more relationships between functional connectivity and multidomain cognitive performance than A β across all AD stages and spanning a wider range of cognitive domains.

6.3 Methods and Data Analysis

6.3.1 Methods

6.3.1.1 Study Design

As described in Chapters 4 and 5.

6.3.1.2 Study Participants

Of the original 252 participants included in Chapters 4 and 5, cognitive test data was available for 185 participants (73.41%), with 124 (67.03%) being CU, 49 (26.49%) MCI, and 12 (6.49%) DAT.

6.3.2 Data Analysis

6.3.2.1 Moderation Analyses

6.3.2.1.1 Independent Variable: Group-Level functional connectivity

Chapter 5 revealed functional connectivity differences between two out of three group comparisons. Specifically, Multivariate Pattern Analysis identified the left thalamus and precuneus as seed regions explaining the most variance between CU and DAT participants and the left thalamus, precuneus, and sub-regions of the superior frontal gyri as seed regions explaining the most variance between MCI and DAT participants.

Next, seed-based connectivity analyses were run to measure whether these seed regions showed group-level functional connectivity differences to the other areas within the brain. Resulting in 13 functional connections as follows:

No significant differences in functional connectivity were observed between CU and MCI participants (group comparison one), and therefore, seed-based connectivity analysis was not performed.

Next, when comparing CU and DAT (group comparison two) functional connectivity:

1. Functional connectivity was higher among CU compared to DAT between the left thalamus [peak MNI coordinates = -06, -08, 00] and right inferior temporal gyrus [peak MNI coordinates = +56, +02, -35].

2. Functional connectivity was higher among DAT compared to CU between the left thalamus [peak MNI co-ordinates = -06, -08, 00] and right inferior frontal gyrus (triangularis) [peak MNI coordinates = +46, +32, +28].
3. Functional connectivity was higher among DAT for the functional connection between the left thalamus [peak MNI coordinates = -06, -08, 00] and the right postcentral gyrus [peak MNI coordinates = +52, -12, +30].
4. Functional connectivity was higher among CU for the functional connection between the precuneus and left precentral gyrus [peak MNI coordinates = -52, -02, +20].
5. Functional connectivity was higher among CU for the functional connection between the precuneus and middle occipital gyrus [peak MNI coordinates = -38, -92, -08].
6. Functional connectivity was higher among CU for the functional connection between the precuneus and left insula [peak MNI coordinates = -29, +10, -16].
7. Functional connectivity was higher among DAT, compared to CU between the precuneus and right precentral gyrus [peak MNI coordinates = +32, -08, +48].

Finally, when comparing functional connectivity between MCI and AD participants:

8. Functional connectivity was higher among DAT for the functional connection between the left thalamus [peak MNI coordinates = -07, -26, +02] and left Crus II [peak MNI coordinates = -38, -75, -35].
9. Functional connectivity was higher among MCI compared to DAT between the right superior frontal gyrus [peak MNI coordinates = +10, +60, +36] and right Rolandic operculum [peak MNI coordinates = +58, +10, +08].
10. Functional connectivity was higher among MCI compared to DAT between the left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and the right middle frontal gyrus [peak MNI coordinates = +44, +38, +18].
11. Functional connectivity was higher among MCI compared to DAT between the left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04].

12. Functional connectivity was higher among MCI For the functional connection between the precuneus and left superior temporal gyrus [peak MNI coordinates = -42, -12, -06].
13. Functional connectivity was higher among DAT for the functional connection between the precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50].

6.3.2.1.2 Dependent Variable: Multi-Domain Cognitive Performance

ADNI's NEUROBAT, a neuropsychological assessment battery that measures short-term (immediate) episodic memory and long-term (delayed) episodic memory, visuospatial processing, language, and executive function, was used to measure cross-sectional measures of multidomain cognitive performance.

6.3.2.1.3 Moderator: AD Biomarkers

To extract regional-level A β and tau information, this data was extracted from the ADNI LONI website. For moderation models, regional A β and tau information were extracted for each brain region cited above (Multivariate Pattern Analysis seeds and functional connections to other brain regions). Regional A β and tau information were therefore used as moderators.

PROCESS (Model 1; see Figure 6.1.), run in SPSS, was used for moderation analyses. This toolbox includes bootstrapping methods for generating confidence intervals for indirect effects.

First, the main effect between functional connectivity (X) and a cognitive domain (Y) must be statistically significant to test a hypothesis. If insignificant, the proposed moderation effect of A β or tau (M) was not further examined with an interaction term in the regression model.

Moderation steps were as follows:

1. Extract statistically significant functional connections between CU and DAT and MCI and DAT as identified using a combination of Multivariate Pattern Analysis and seed-based connectivity analysis (Chapter 5) as the independent variables (X) in moderation analyses.

Resulting in 13 functional connections (seven between CU and DAT and six between MCI and DAT).

2. Take multidomain cognitive performance scores for all domains (immediate and delayed episodic memory, visuospatial processing, language, and executive function) as the dependent variables in moderation analyses (Y). Resulting in five scores per functional connection.
3. Take regional $A\beta$ and tau values for each brain region in each functional connection as moderators (M) in moderation analyses, e.g., left thalamus ($A\beta$), left thalamus (tau), right inferior temporal gyrus ($A\beta$), and right inferior temporal gyrus (tau) – four measures per functional connection.

Moderation analyses were used to test whether regional $A\beta$ and tau moderate the relationships between functional connectivity and multidomain cognitive performance among CU participants.

In Chapter 5, seven functional connectivity differences were identified between CU and DAT participants and six functional connectivity differences were identified between MCI and DAT participants.

One example of a set of moderation analyses includes the following:

- Left thalamus ($A\beta$) as a moderator (M) in the relationships between left thalamus and right inferior temporal gyrus functional connectivity (X) and multidomain cognitive performance (immediate and delayed episodic memory, visuospatial processing, language, and executive processing (Y)).
- Right inferior temporal gyrus ($A\beta$) as a moderator (M) in the relationships between left thalamus and right inferior temporal gyrus functional connectivity (X) and multidomain cognitive performance (immediate and delayed episodic memory, visuospatial processing, language, and executive processing (Y)).
- Left thalamus (tau) as a moderator (M) in the relationships between left thalamus and right inferior temporal gyrus functional connectivity (X) and multidomain cognitive performance

(immediate and delayed episodic memory, visuospatial processing, language, and executive processing (Y)).

- Right inferior temporal gyrus (τ) as a moderator (M) in the relationships between left thalamus and right inferior temporal gyrus functional connectivity (X) and multidomain cognitive performance (immediate and delayed episodic memory, visuospatial processing, language, and executive processing (Y)).

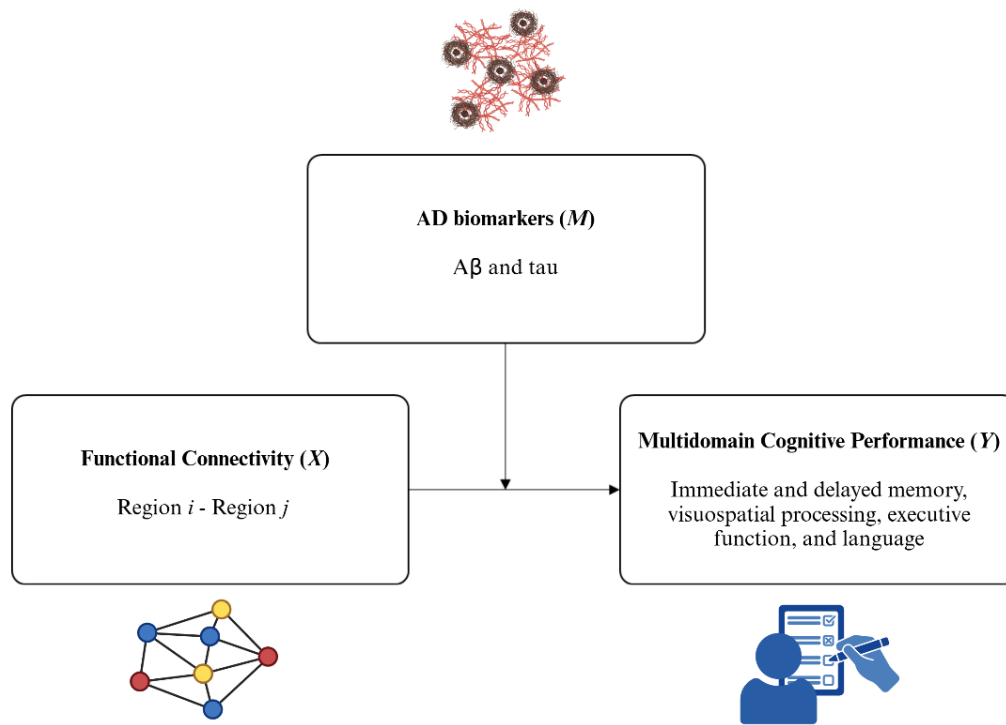


Figure 6.1. Expanded simple moderation model with examples.

Note: whereby M = moderator (regional A β and tau), X = functional connectivity, and Y = cognitive performance; i and j = two separate brain regions that demonstrate functional connectivity.

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A combination of Multivariate Pattern Analysis and seed-based connectivity analyses revealed seven functional connections when comparing CU vs. DAT and six functional connections when comparing MCI vs. DAT (13 functional connections total). Figure 6.2. provides an example of one set of moderation models for one function connection – to explore the potential relationships between regional (and local) A β load (denoted in Figure 6.2. as 1. and 3.) and regional tau load (2. and 4.) on functional connectivity (5.) and multidomain cognitive performance (6-10.).

Each moderation model set was constructed based on which functional connections were extracted for each cohort. For example, among CU participants, seven functional connections were significantly different between CU and DAT participants. Six functional connections were significantly different

between MCI and DAT participants. This resulted in all 13 functional connections being pertinent for DAT participants.

Importantly, many hypotheses were tested due to the exploratory nature of these analyses. Consequently, we anticipated no significant effects would survive multiple test corrections at this scale. Nonetheless, any significant impacts that emerge could inform more targeted approaches in future studies, focusing on functional connections that explain the most variance between DAT groups.

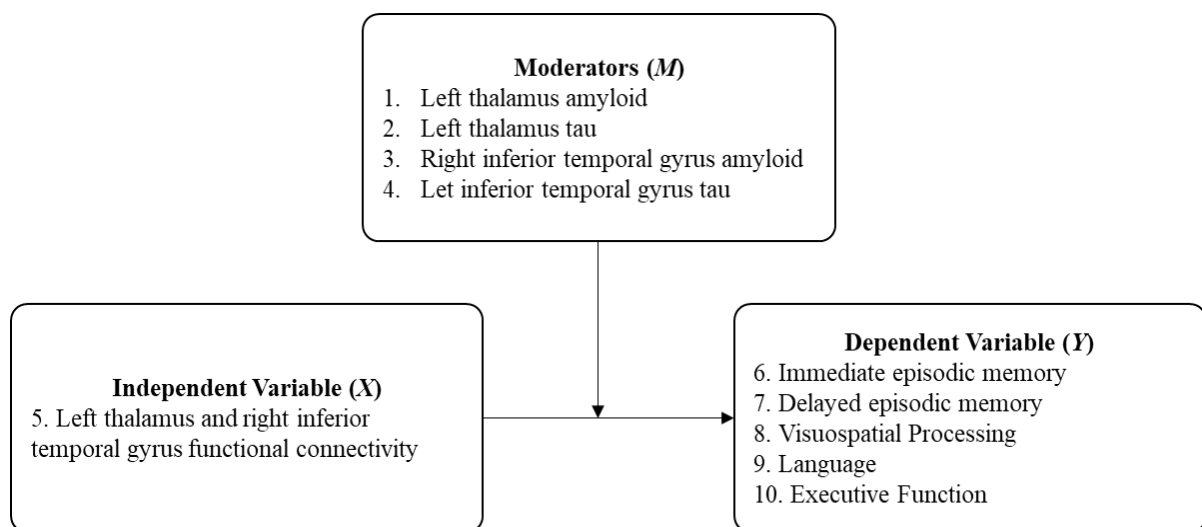


Figure 6.2. Overview of how simple moderation analysis models were constructed for each functional connection to explore the potential modifying effects between regional A β and tau load

Note: example of how A β load (1. and 3.) and regional/local tau load (2. and 4.) moderate (*M*) the relationships between functional connectivity (5.) (*X*) and multidomain cognitive performance (6-10.) (*Y*).

6.4 Results

The results included in-text pertain to incidences whereby $A\beta$ / tau were significant moderators of the relationship(s) between functional connectivity and cognitive performance ($p < .05$). All other relationships were not statistically significant ($p > .05$). A conceptual illustration detailing how these interactions were interpreted can be found in Figure 6.3. Summaries can be found in Figures 6.4. and 6.5. and Tables 6.3. and 6.4. Figures 6.6a. – m. shows the specific relationships in detail.

6.4.1 Cognitive Performance

See Table 6.1. for cognitive performance results.

Table 6.1. Descriptive statistics for neuropsychological assessment cognitive domain scores between stages

Cognitive Domain		Disease Stage		
		CU	MCI	DAT
		($n = 124$)	($n = 49$)	($n = 12$)
<i>Immediate Episodic Memory</i>	M (<i>SD</i>)	41.90 (11.20)	41.92 (12.60)	43.83 (11.93)
<i>Delayed Episodic Memory</i>	M (<i>SD</i>)	6.44 (4.28)	7.20 (4.90)	6.83 (4.53)
<i>Visuospatial Processing</i>	M (<i>SD</i>)	9.45 (1.14)	9.16 (1.65)	9.25 (1.29)
<i>Executive Function</i>	M (<i>SD</i>)	83.19 (44.63)	86.17 (51.70)	90.50 (68.94)
<i>Language</i>	M (<i>SD</i>)	49.81 (9.44)	47.24 (10.40)	48.50 (7.42)

Notes. CU = cognitively unimpaired; MCI = mild cognitive impairment; DAT = dementia due to Alzheimer's Disease; M = mean; *SD* = standard deviation.

6.4.2 CU Interaction Models: AD biomarkers as a moderator of functional connectivity and multidomain cognitive performance

6.4.2.1 A β as a Moderator Among CU Participants

Moderation analysis was used to test the hypothesis that left insula A β moderates the relationship between precuneus and left insula [peak MNI coordinates = -29, +10, -16] functional connectivity and visuospatial processing among CU participants (see Figure 6.6a). These variables accounted for significant variance in visuospatial processing, $R^2 = .09$, $F(1, 120) = 3.76$, $p = .013$. The interaction between precuneus and left insula functional connectivity and left insula A β was also significant, $\Delta R^2 = .04$, $F(1, 120) = 5.57$, $p = .020$.

The interaction plot (see Figure 6.6a.) demonstrates a moderating effect of precuneus A β load (M) on the relationship between precuneus and left insula functional connectivity (X) and visuospatial processing (Y). Specifically, for individuals with lower levels of precuneus A β , visuospatial processing increased as functional connectivity (between the precuneus and left insula) increased. Conversely, for individuals with higher levels of precuneus A β , visuospatial processing decreased as functional connectivity (between the precuneus and left insula) increased.

6.4.2.2 Tau as a Moderator Among CU Participants

Moderation analysis was used to test the hypothesis that precuneus tau moderates the relationship between the precuneus and right precentral gyrus [peak MNI coordinates = +32, -08, +48] functional connectivity and visuospatial processing among CU participants (see Figure 6.6b.). These variables accounted for significant variance in visuospatial processing, $R^2 = .376$, $F(3, 120) = 6.57$, $p < .001$. Next, the interaction term between precuneus and right precentral gyrus functional connectivity was added to the regression model, which did account for a significant proportion of variance in visuospatial processing, $\Delta R^2 = .05$, $F(1, 120) = 6.99$, $p = .009$.

The interaction plot (see Figure 6.6b.) shows a moderating effect, with precuneus tau load moderating (M) the relationship between precuneus and right precentral functional connectivity (X) and visuospatial processing (Y). For individuals with lower levels of precuneus tau, visuospatial processing increased as

functional connectivity between the precuneus and right precentral gyrus increased. However, visuospatial processing decreased for individuals with higher levels of precuneus tau as functional connectivity between the precuneus and right precentral increased.

Secondly, moderation analysis was used to test the hypothesis that right precentral gyrus tau moderates the relationship between the precuneus and right precentral gyrus [peak MNI coordinates = +32, -08, +48] functional connectivity and visuospatial processing among CU participants (see Figure 6.6c.). These variables accounted for significant variance in visuospatial processing, $R^2 = .21$, $F(3, 120) = 10.38$, $p < .001$. Next, the interaction term between the precuneus and right precentral gyrus functional connectivity and right precentral gyrus tau was added to the regression model, which did account for a significant proportion of variance in visuospatial processing, $\Delta R^2 = .05$, $F(1, 120) = 7.57$, $p = .007$. In the interaction plot (see Figure 6.6c.), right precentral gyrus tau moderated (M) the relationship between precuneus and right precentral gyrus functional connectivity (X) and visuospatial processing (Y). For individuals with lower levels of right precentral gyrus tau, visuospatial processing increased as functional connectivity increased. In contrast, for individuals with higher levels of right precentral gyrus tau, visuospatial processing decreased as functional connectivity increased.

Lastly, moderation analysis was used to explore the role of precuneus tau as a moderator on the relationship between the precuneus and left precentral gyrus [peak MNI coordinates = -52, -02, +20] functional connectivity and visuospatial processing among CU participants (see Figure 6.6d.). The model did explain a significant amount of variance, $R^2 = .12$, $F(1, 120) = 5.53$, $p = .001$. The interaction between precuneus and left precentral gyrus functional connectivity and precuneus tau was also significant, $\Delta R^2 = .030$, $F(1, 120) = 4.04$, $p = .047$.

In the interaction plot (see Figure 6.6d.), precuneus tau moderated (M) the relationship between precuneus and left precentral gyrus functional connectivity (X) and visuospatial processing (Y). For individuals with lower levels of precuneus tau, visuospatial processing increased as functional connectivity between the precuneus and left precentral gyrus increased. In contrast, for individuals with

higher levels of precuneus tau, visuospatial processing decreased as functional connectivity between the precuneus and left precentral gyrus increased.

6.4.3 MCI Interaction Models: AD biomarkers as a moderator of functional connectivity and multidomain cognitive performance

6.4.3.1 A β as a Moderator Among MCI Participants

The model was used to test whether left superior frontal gyrus A β moderates the relationship between the left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity and delayed episodic memory among MCI participants (see Figure 6.6e.). The model was significant, $R^2 = .22$, $F(3, 45) = 4.15$, $p = .011$. The interaction was also significant, $\Delta R^2 = .07$, $F(1, 45) = 4.26$, $p = .045$.

The interaction plot (see Figure 6.6e.) shows a moderating effect, with left superior frontal gyrus A β load moderating (M) the relationships between left superior frontal gyrus and left putamen functional connectivity (X) and delayed episodic memory (Y). For individuals with lower left superior frontal gyrus A β load, delayed episodic memory decreased as functional connectivity increased. However, delayed episodic memory increased as functional connectivity increased for individuals with higher left superior frontal gyrus A β load levels.

Next, the model was used to test whether left putamen A β moderates the relationship between the left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity and delayed episodic memory among MCI participants (see Figure 6.6f.). The model was significant, $R^2 = .22$, $F(3, 45) = 4.25$, $p = .010$. The interaction was also significant, $\Delta R^2 = .10$, $F(1, 45) = 5.72$, $p = .021$.

The interaction plot (see Figure 6.6f.) shows a moderating effect, with left putamen A β load moderating (M) the relationships between left superior frontal gyrus and left putamen functional connectivity (X) and delayed episodic memory (Y) for individuals with lower levels of left putamen A β load, delayed episodic memory was found to decrease as functional connectivity increased. However, delayed

episodic memory increased as functional connectivity increased for individuals with higher left superior frontal gyrus A β load levels.

The model was used to test whether the precuneus A β moderates the relationship between the precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity and visuospatial processing among MCI participants (see Figure 6.6g.). The model was significant, $R^2 = .18$, $F(3, 45) = 3.30$, $p = .029$. The interaction was also significant, $\Delta R^2 = .11$, $F(1, 45) = 5.86$, $p = .020$.

The interaction plot (see Figure 6.6g.) shows a moderating effect, with precuneus A β load moderating (M) the relationships between precuneus and left superior temporal gyrus (posterior portion) functional connectivity (X) and visuospatial processing (Y). For individuals with lower levels of precuneus A β load, visuospatial processing decreased as functional connectivity increased. However, visuospatial processing was found to increase for individuals with higher levels of precuneus A β load as functional connectivity increased.

Lastly, the model was used to test whether left superior temporal gyrus A β moderates the relationship between the precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity and visuospatial processing among MCI participants (see Figure 6.6h.). The model was significant, $R^2 = .22$, $F(3, 45) = 4.14$, $p = .011$. As was the interaction, $\Delta R^2 = .11$, $F(1, 45) = 6.37$, $p = .015$.

The interaction plot (see Figure 6.6h.) shows a moderating effect, with left superior temporal gyrus A β load moderating (M) the relationships between the precuneus and left superior temporal gyrus (posterior portion) functional connectivity (X) and visuospatial processing (Y). For individuals with lower left superior temporal gyrus A β load, visuospatial processing decreased as functional connectivity increased. However, for individuals with higher levels of left superior temporal gyrus A β load, visuospatial processing increased as functional connectivity increased.

6.4.3.2 Tau as a Moderator Among MCI Participants

The model was used to test whether precuneus tau moderates the relationship between the precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50] functional connectivity and executive function among MCI participants (see Figure 6.6i.). The model was significant, $R^2 = .36$, $F(3, 45) = 8.44$, $p < .001$. As was the interaction, $\Delta R^2 = .17$, $F(1, 45) = 9.43$, $p = .004$.

The interaction plot (see Figure 6.6i.) shows a moderating effect, with precuneus tau load moderating (M) the relationships between precuneus and left precentral gyrus functional connectivity (X) and executive function (Y). For individuals with lower levels of precuneus tau load, executive function decreased as functional connectivity increased. However, executive function increased as functional connectivity increased for individuals with higher levels of precuneus tau load.

Moderation analysis was used to test the hypothesis that left precentral gyrus tau moderates the relationship between the precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50] functional connectivity and executive function among MCI participants (see Figure 6.6j.). These variables did account for a significant amount of variance in executive function, $R^2 = .39$, $F(3, 45) = 9.62$, $p < .001$. The interaction was also significant, $\Delta R^2 = .18$, $F(1, 45) = 13.20$, $p = .001$.

The interaction plot (see Figure 6.6j.) shows a moderating effect, with left precentral gyrus tau load moderating (M) the relationships between precuneus and left precentral gyrus functional connectivity (X) and executive function (Y). For individuals with lower left precentral gyrus tau load levels, executive function decreased as functional connectivity increased. However, executive function increased as functional connectivity increased for individuals with higher left precentral gyrus tau load levels.

The model was used to test whether left putamen tau moderates the relationship between the left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity and delayed episodic memory, among MCI participants (see Figure 6.6k.). The model was significant, $R^2 = .20$, $F(3, 45) = 3.66$, $p = .019$. The interaction was also significant, $\Delta R^2 = .17$, $F(1, 45) = 9.43$, $p = .004$.

The interaction plot (see Figure 6.6k.) shows a moderating effect, with left putamen tau load moderating (*M*) the relationships between left superior frontal gyrus and left putamen functional connectivity (*X*) and delayed episodic memory (*Y*) among MCI participants for individuals with lower levels of left putamen tau load, delayed episodic memory was found to increase as functional connectivity increased. However, for individuals with higher levels of left putamen tau load, delayed episodic memory decreased as functional connectivity increased.

The model was used to test whether precuneus tau moderates the relationship between the precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity and visuospatial processing among MCI participants (see Figure 6.6l.). The model was significant, $R^2 = .21$, $F(3, 45) = 3.91$, $p = .015$. As was the interaction, $\Delta R^2 = .08$, $F(1, 45) = 4.32$, $p = .043$.

The interaction plot (see Figure 6.6l.) shows a moderating effect, with precuneus tau load moderating (*M*) the relationship between the precuneus and left superior temporal gyrus (posterior portion) functional connectivity (*X*) and visuospatial processing (*Y*) among MCI participants. For individuals with lower levels of precuneus tau load, visuospatial processing decreased as functional connectivity increased. However, visuospatial processing was found to increase for individuals with higher levels of precuneus tau load as functional connectivity increased.

6.4.4 DAT Interaction Models: AD biomarkers as a moderator of functional connectivity and multidomain cognitive performance

6.4.4.1 A β as a Moderator Among DAT Participants

No significant effects were observed across all models.

6.4.4.2 Tau as a Moderator Among DAT Participants

No significant effects were observed across all models.

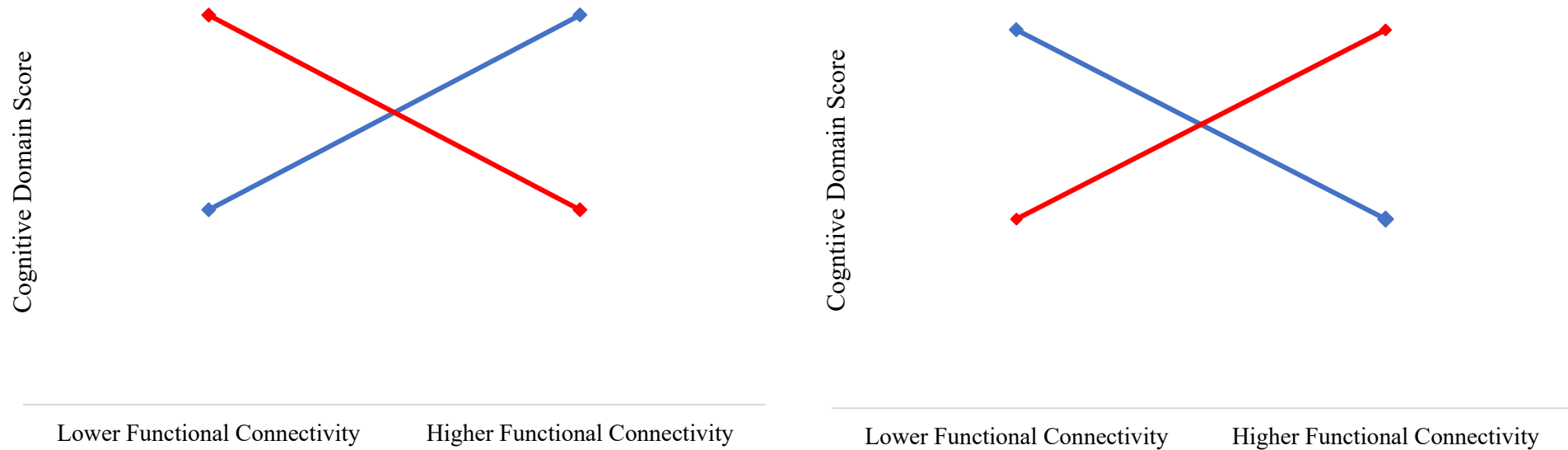


Figure 6.3. Conceptual figure illustrating an interaction effect of $A\beta$ / tau on the relationship between functional connectivity and cognitive performance

Note: *Left:* The X-axis represents lower vs. higher levels of functional connectivity. The blue line represents lower levels of amyloid-beta ($A\beta$) / tau, in which the measured outcome (e.g., cognition) increases as functional connectivity increases, and the red line represents higher levels of $A\beta$ / tau, in which the measured outcome (e.g., cognition) decreases as functional connectivity increases.

Right: The X-axis represents lower vs. higher levels of functional connectivity. The blue line represents lower levels of $A\beta$ / tau, in which the measured outcome (e.g., cognition) decreases as functional connectivity increases, and the red line represents higher levels of $A\beta$ / tau, in which the measured outcome (e.g., cognition) increases as functional connectivity increases.

6.4.5 Multiple Test Corrections

Although multiple statistically significant results suggest the roles of regional A β and tau as modifiers in the relationships between various functional connections and cognitive domains, multiple test corrections (Bonferroni and Benjamini-Hochberg's procedure for controlling the FDR) resulted in no significant findings. This suggests that none of the p -values were small enough to pass the threshold set by Bonferroni and Benjamini-Hochberg when controlling for error rates across many hypotheses. Therefore, regardless of the exploratory nature of these analyses, all significant results must be interpreted with caution.

		Aβ as a Moderator ...					Tau as a Moderator ...				
		of functional connectivity (X)			and Cognition (Y)		of functional connectivity (X)			and Cognition (Y)	
		Immediate Memory	Delayed Memory	Visuospatial Processing	Language	Executive Function	Immediate Memory	Delayed Memory	Visuospatial Processing	Language	Executive Function
Functional Connections	Left thalamus and right inferior temporal gyrus										
	Left thalamus and right inferior frontal gyrus (pars triangularis)										
	Left thalamus and right postcentral gyrus										
	Precuneus and left precentral gyrus								Precuneus		
	Precuneus and left middle occipital gyrus										
	Precuneus and insula			left insula							
	Precuneus and right precentral gyrus								Precuneus <u>and</u> right precentral gyrus		

Figure 6.4. A β and tau as a statistically significant modifiers of functional connectivity and cognitive performance among CU

Note: A β / tau as significant moderators between functional connectivity and cognition. These relationships did not survive multiple test corrections.

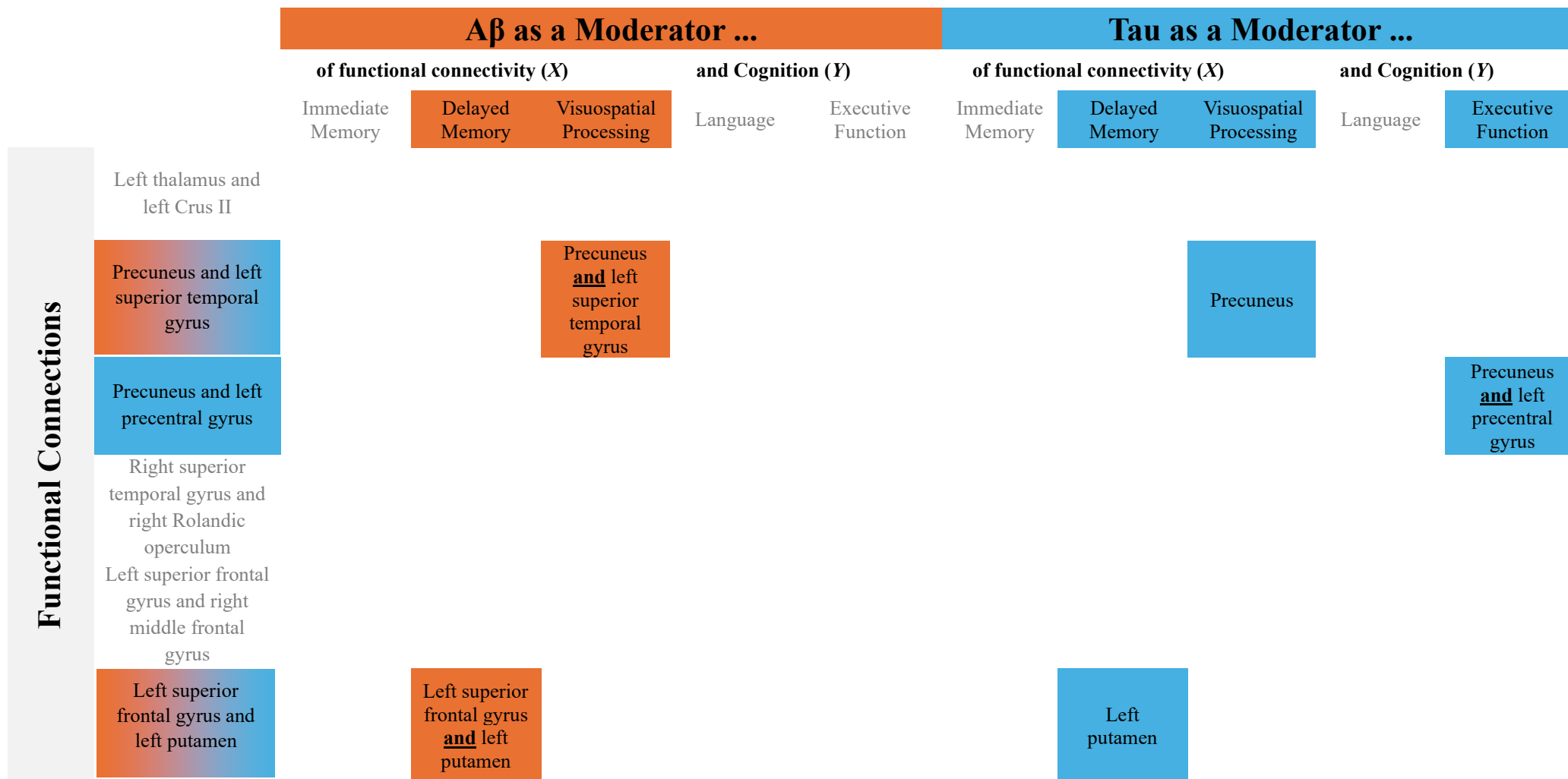


Figure 6.5. Aβ and tau as a statistically significant modifiers of functional connectivity and cognitive performance among MCI

Note: Aβ / tau as significant moderators between functional connectivity and cognition. These relationships did not survive multiple test corrections.

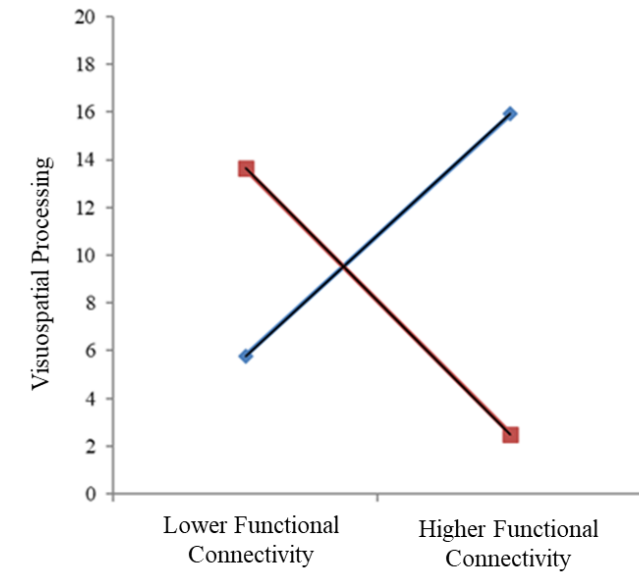
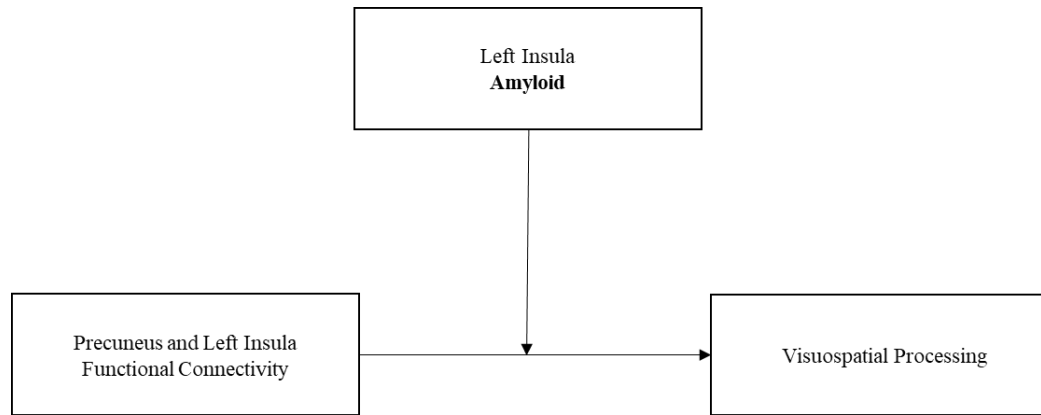


Figure 6.6a. Simple moderation model and interaction plot

Note: *Left*: Among cognitively unimpaired (CU) participants, **left insula amyloid-beta ($A\beta$) load** was found to moderate (M) on the relationship between the precuneus and left insula [peak MNI coordinates = -29, +10, -16] functional connectivity (X) and visuospatial processing (Y).

Right: An interaction plot showing the moderating effect of **precuneus $A\beta$ load**, which was found to moderate (M) the relationship between precuneus and left insula [peak MNI coordinates = -29, +10, -16] functional connectivity (X) and visuospatial processing (Y) among CU participants. For CU participants with lower levels of precuneus $A\beta$ (**blue**), visuospatial processing increased as functional connectivity between the precuneus and right precentral gyrus increased. However, for individuals with higher levels of precuneus tau (**red**), visuospatial processing decreased as functional connectivity between the precuneus and right precentral increased.

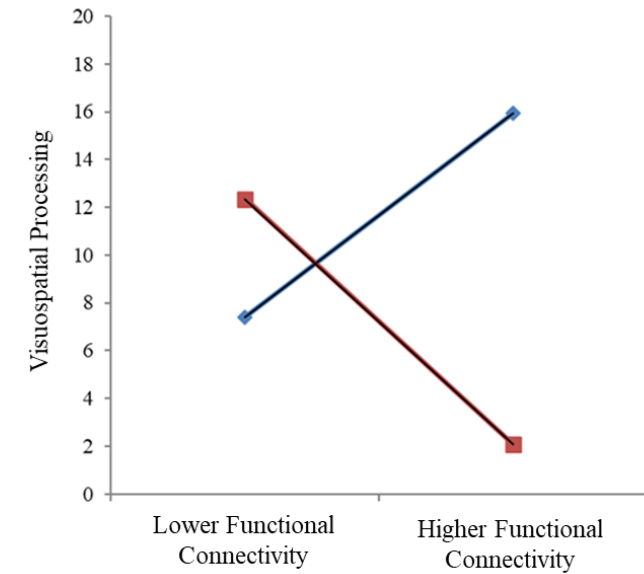
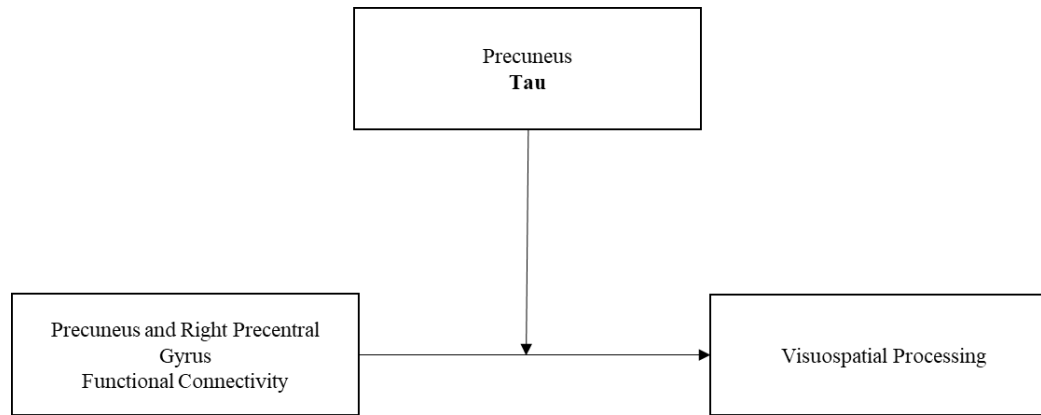


Figure 6.6b. Simple moderation model and interaction plot

Left: Among cognitively unimpaired (CU) participants, **precuneus tau load** was found to moderate (*M*) the relationship between precuneus and right precentral [peak MNI coordinates = +32, -08, +48] functional connectivity (*X*) and visuospatial processing (*Y*).

Right: An interaction plot showing the moderating effect of **precuneus tau load**, which was found to moderate (*M*) on the relationship between precuneus and right precentral [peak MNI coordinates = +32, -08, +48] functional connectivity (*X*) and visuospatial processing (*Y*) among CU participants. For CU participants with lower levels of precuneus tau (**blue**), visuospatial processing increased as functional connectivity between the precuneus.

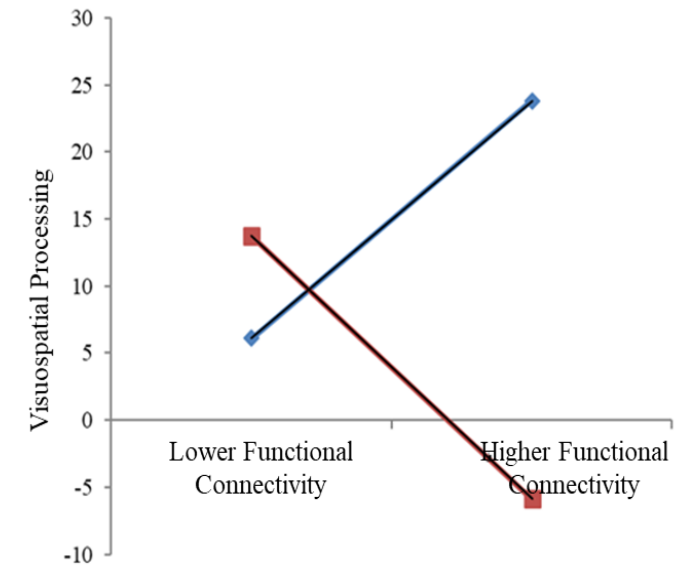
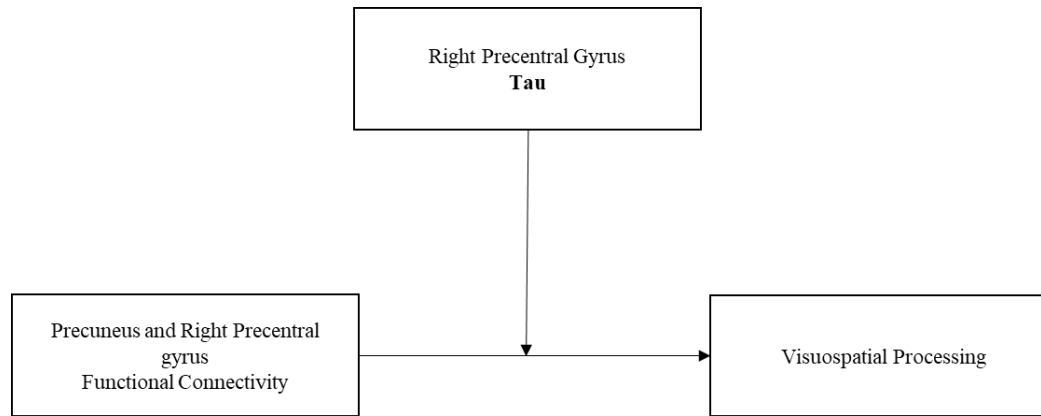


Figure 6.6c. Simple moderation model and interaction plot

Left: Among cognitively unimpaired (CU) participants, **right precentral gyrus tau load** was found to moderate (*M*) the relationship between precuneus and right precentral gyrus [peak MNI coordinates = +32, -08, +48] functional connectivity (*X*) and visuospatial processing (*Y*).

Right: An interaction plot showing the moderating effect of **right precentral tau load**, which was found to (*M*) on the relationship between precuneus and right precentral [peak MNI coordinates = +32, -08, +48] functional connectivity (*X*) and visuospatial processing (*Y*) among CU participants. For CU participants with lower levels of right precentral tau (**blue**), visuospatial processing increased as functional connectivity between the precuneus and right precentral gyrus increased. However, for individuals with higher levels of right precentral gyrus tau (**red**), visuospatial processing decreased as functional connectivity between the precuneus and right precentral gyrus increased.

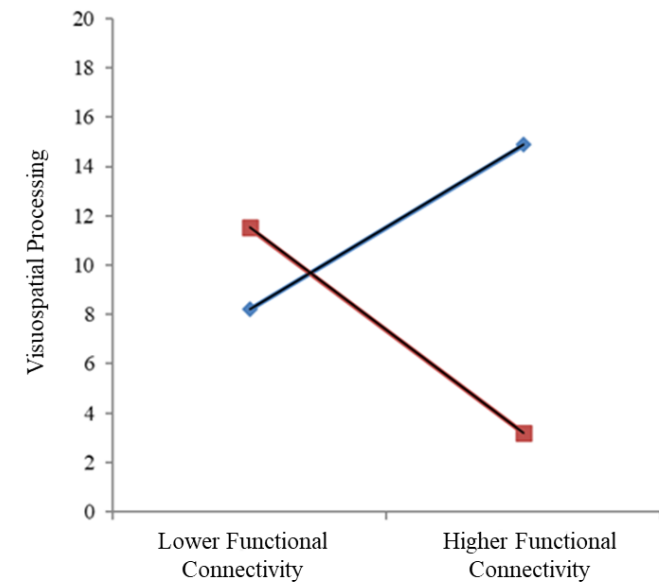
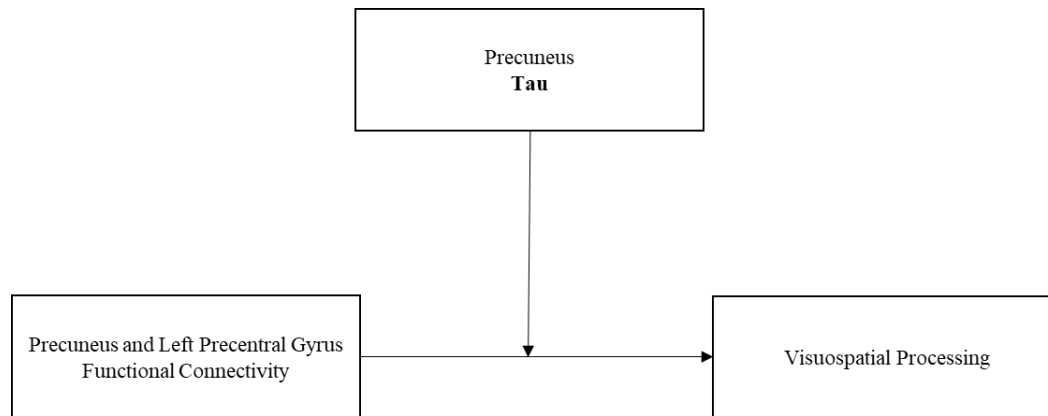


Figure 6.6d. Simple moderation model and interaction plot

Note: *Left*: Among cognitively unimpaired (CU) participants, **precuneus tau load** was found to moderate (*M*) the relationship between precuneus and left precentral gyrus [peak MNI coordinates = -52, -02, +20] functional connectivity (*X*) and visuospatial processing (*Y*).

Right: An interaction plot showing the moderating effect of **precuneus tau load**, which was found to moderate (*M*) on the relationship between precuneus and left precentral [peak MNI coordinates = -52, -02, +20] functional connectivity (*X*) and visuospatial processing (*Y*) among CU participants. For CU participants with lower levels of precuneus tau (**blue**), visuospatial processing increased as functional connectivity between the precuneus and left precentral gyrus increased. However, for individuals with higher levels of precuneus tau (**red**), visuospatial processing decreased as functional connectivity between the precuneus and left precentral gyrus increased.

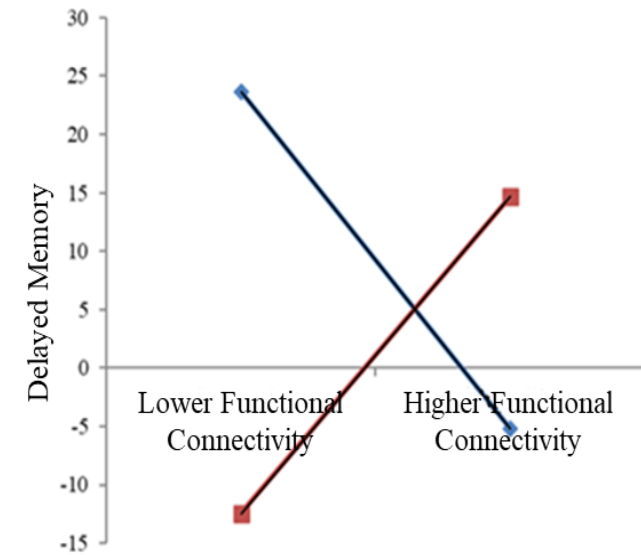
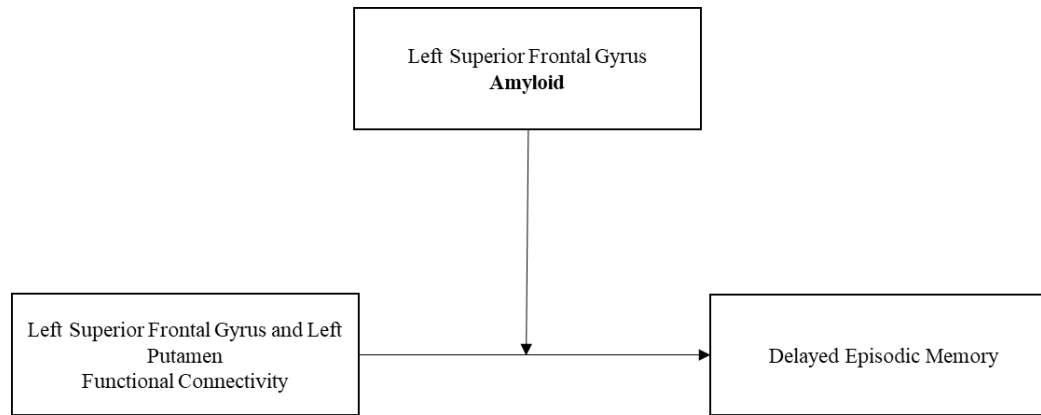


Figure 6.6e. Simple moderation model and interaction plot

Note: *Left:* Among mild cognitive impairment (MCI) participants, **left superior frontal gyrus amyloid-beta ($A\beta$) load** was found to moderate (*M*) the relationship between left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity (*X*) and delayed episodic memory (*Y*).

Right: An interaction plot showing the moderating effect of **left superior frontal gyrus $A\beta$ load**, which was found to moderate (*M*) on the relationship between left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity (*X*) and delayed episodic memory (*Y*) among participants with MCI. For MCI participants with lower levels of left superior frontal gyrus $A\beta$ (**blue**), delayed episodic memory was found to decrease as functional connectivity between the left superior frontal gyrus and left putamen increased; however, for individuals with higher levels of left superior frontal gyrus $A\beta$ (**red**), delayed episodic memory increased as functional connectivity between the left superior frontal gyrus and left putamen increased.

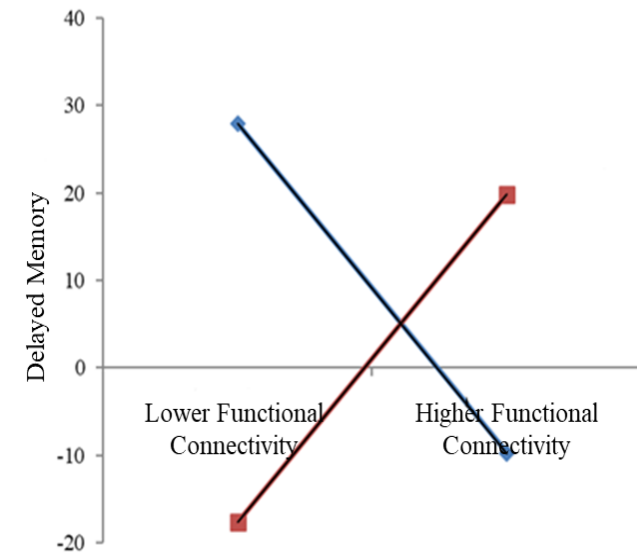
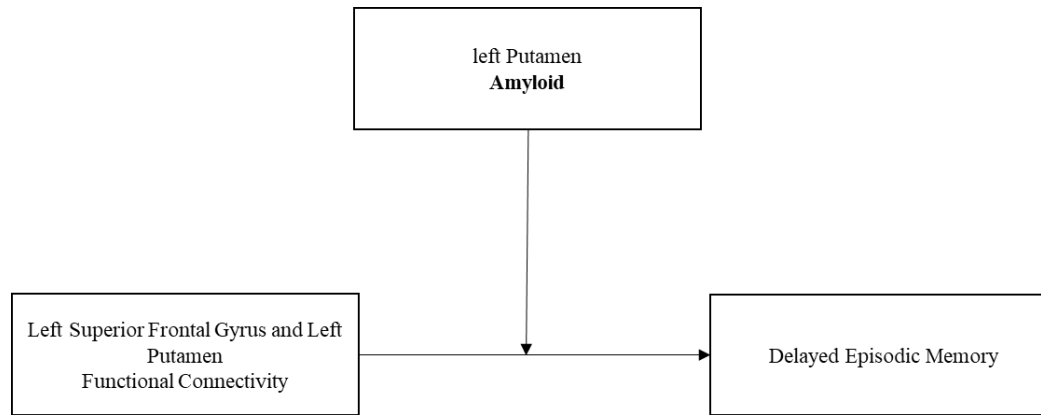


Figure 6.6f. Simple moderation model and interaction plot

Note: *Left:* Among mild cognitive impairment (MCI) participants, **left putamen amyloid-beta ($A\beta$) load** was found to moderate (*M*) the relationship between left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity (*X*) and delayed episodic memory (*Y*).

Right: An interaction plot showing the moderating effect of **left putamen $A\beta$ load**, which was found to moderate (*M*) on the relationship between left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity (*X*) and delayed episodic memory (*Y*) among participants with MCI. For MCI participants with lower levels of left putamen $A\beta$ (blue), delayed episodic memory decreased as functional connectivity between the left superior frontal gyrus and left putamen increased. However, for individuals with higher levels of left putamen $A\beta$ (red), delayed episodic memory increased as functional connectivity between the left superior frontal gyrus and left putamen increased.

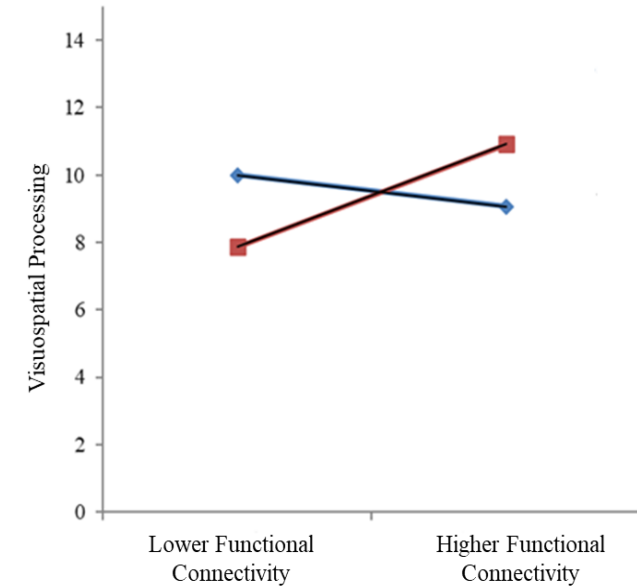
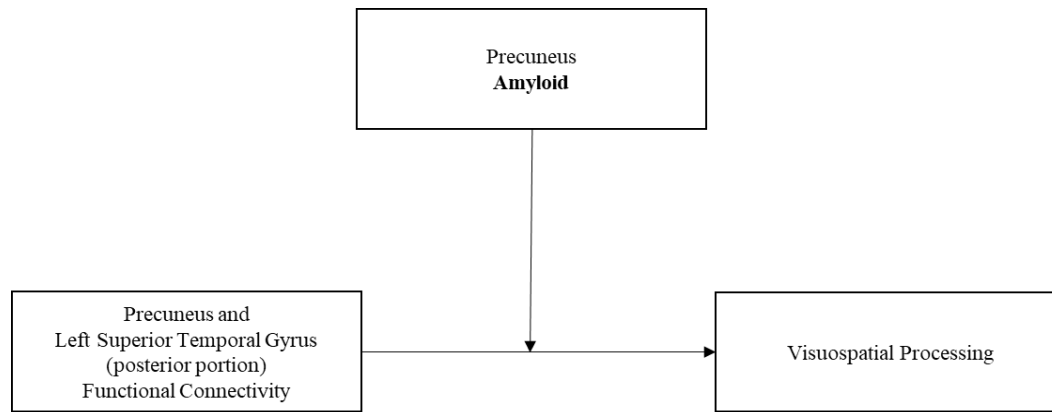


Figure 6.6g. Simple moderation model and interaction plot

Note: *Left:* Among mild cognitive impairment (MCI) participants, **precuneus amyloid-beta ($A\beta$) load** was found to moderate (*M*) the relationship between precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity (*X*) and visuospatial processing (*Y*).

Right: An interaction plot showing the moderating effect of **precuneus $A\beta$ load**, which was found to moderate (*M*) on the relationship between precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity (*X*) and visuospatial processing (*Y*) among participants with MCI. For MCI participants with lower levels of precuneus $A\beta$ (**blue**), visuospatial processing decreased as functional connectivity between the precuneus and left superior temporal gyrus increased. However, for individuals with higher levels of precuneus $A\beta$ (**red**), visuospatial processing increased as functional connectivity between the precuneus and left superior temporal gyrus increased.

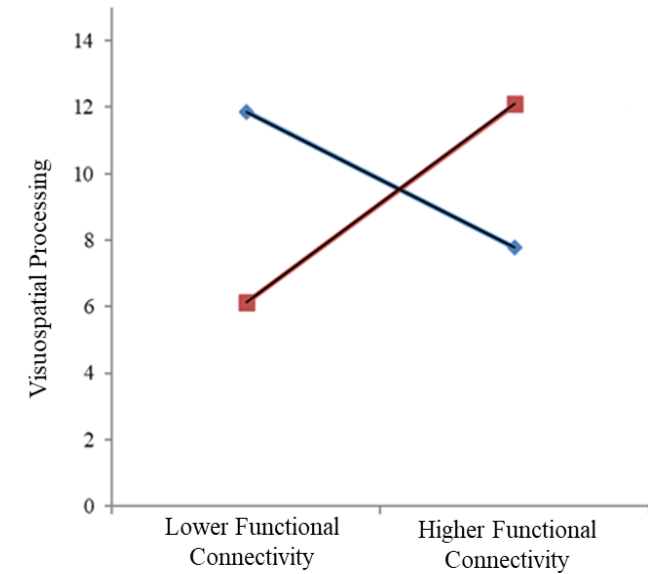
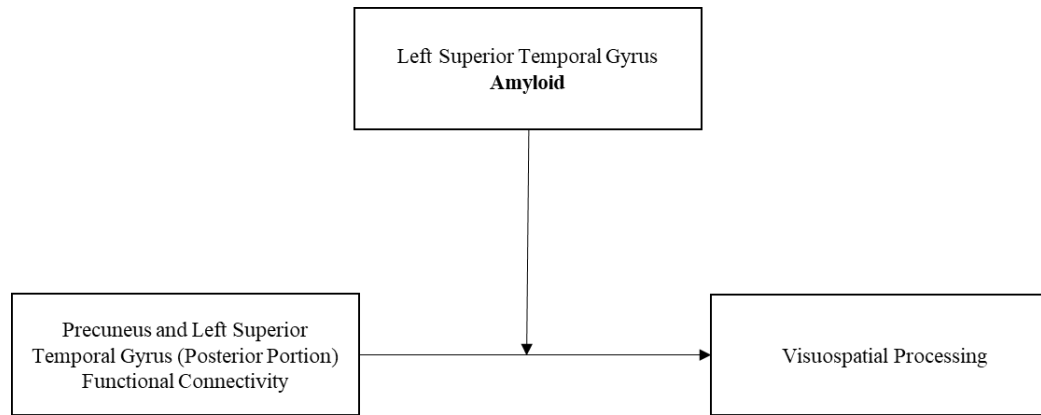


Figure 6.6h. Simple moderation model and interaction plot

Note: *Left:* Among mild cognitive impairment (MCI) participants, **left superior temporal gyrus amyloid-beta ($A\beta$)** load was found to moderate (*M*) the relationship between precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity (*X*) and visuospatial processing (*Y*).

Right: An interaction plot showing the moderating effect of **left superior temporal gyrus $A\beta$** (*M*) on the relationship between precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity (*X*) and visuospatial processing (*Y*) among participants with MCI. For MCI participants with lower left superior temporal gyrus $A\beta$ (**blue**) levels, visuospatial processing decreased as functional connectivity between the precuneus and left superior temporal gyrus (posterior portion) increased. However, for individuals with higher levels of precuneus $A\beta$ (**red**), visuospatial processing increased as functional connectivity between the precuneus and left superior temporal gyrus (posterior portion) increased.

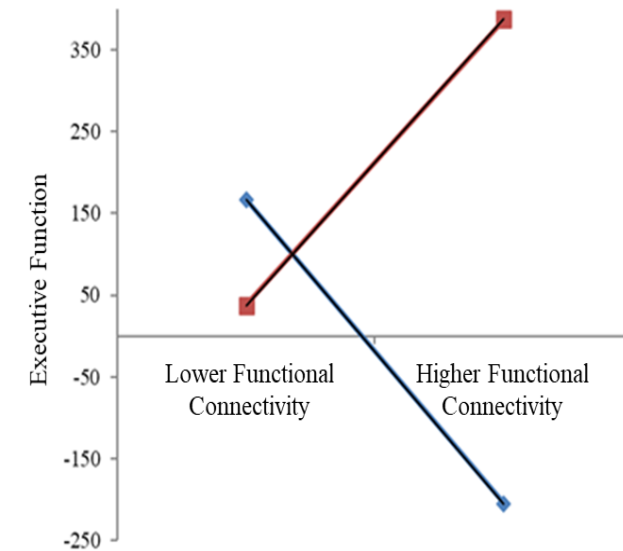
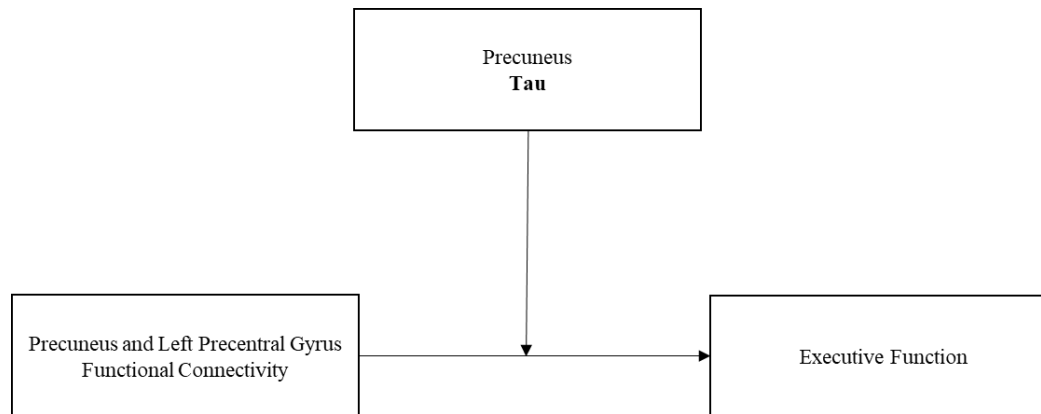


Figure 6.6i. Simple moderation model and interaction plot

Note: *Left*: Among mild cognitive impairment (MCI) participants, **precuneus tau load** moderates (*M*) the relationship between precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50] functional connectivity (*X*) and executive function (*Y*).

Right: An interaction plot showing the moderating effect of **precuneus tau load** (*M*) on the relationship between precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50] functional connectivity (*X*) and executive function (*Y*) among participants with MCI. For MCI participants with lower levels of precuneus tau (**blue**), executive function decreased as functional connectivity between the precuneus and left precentral gyrus increased. However, for individuals with higher levels of precuneus tau (**red**), executive function increased as functional connectivity between the precuneus and left precentral gyrus increased.

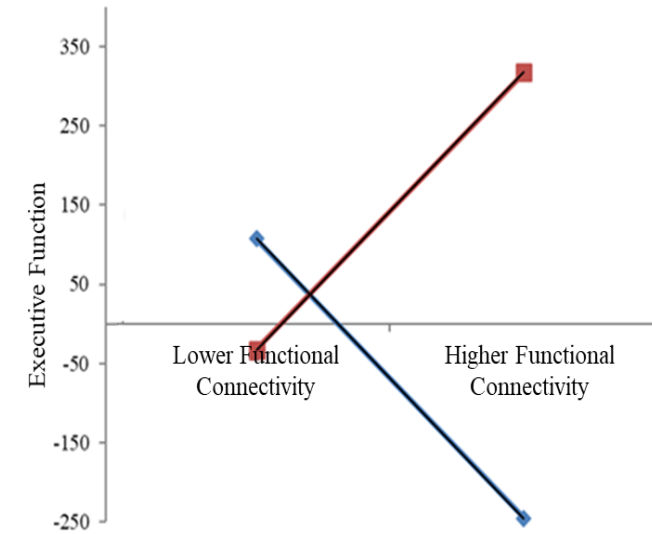
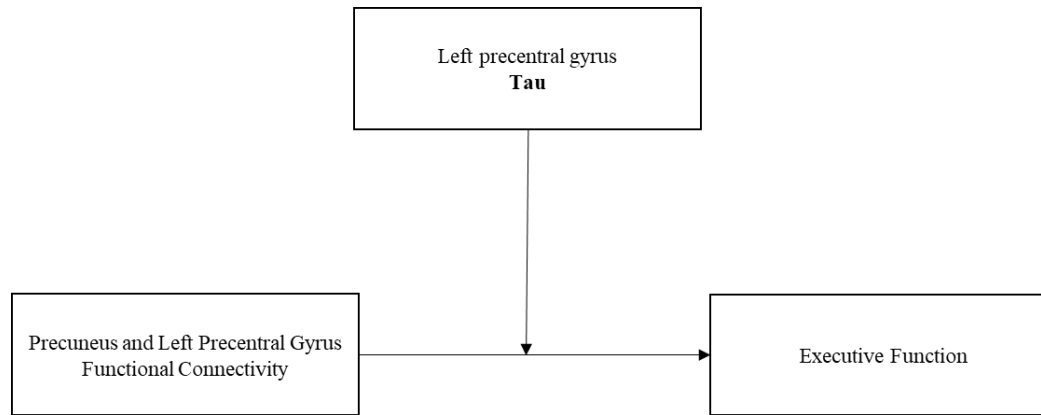


Figure 6.6j. Simple moderation model and interaction plot

Note: *Left*: Among mild cognitive impairment (MCI) participants, **left precentral gyrus tau load** was found to moderate (M) the relationship between the precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50] functional connectivity (X) and executive function (Y).

Right: An interaction plot showing the moderating effect of **left precentral gyrus tau load** (M) on the relationship between precuneus and left precentral gyrus [peak MNI coordinates = -50, -10, +50] functional connectivity (X) and executive function (Y) among participants with MCI. For MCI participants with lower left precentral gyrus tau (**blue**) levels, executive function decreased as functional connectivity between the precuneus and left precentral gyrus increased. However, for individuals with higher levels of left precentral tau (**red**), executive function increased as functional connectivity between the precuneus and left precentral gyrus increased.

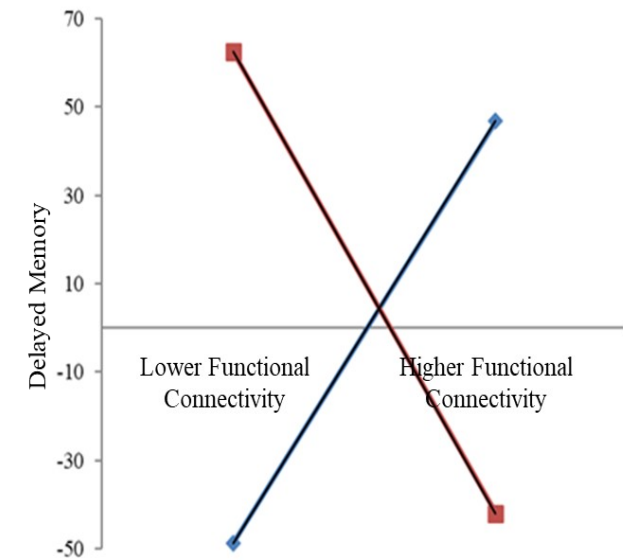
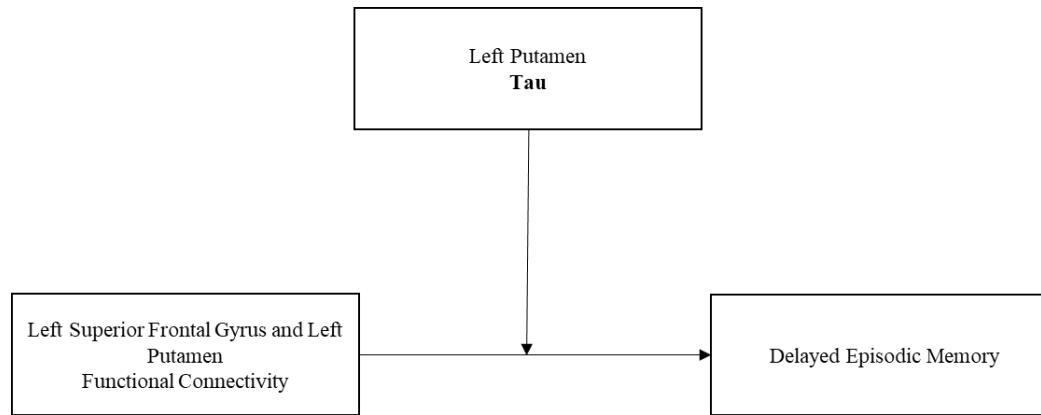


Figure 6.6k. Simple moderation model and interaction plot

Note: *Left:* Among mild cognitive impairment (MCI) participants, **left putamen tau load** was found to moderate (*M*) the relationship between left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity functional connectivity (*X*) and delayed episodic memory (*Y*).

Right: An interaction plot showing the moderating effect of **left putamen tau load** (*M*) on the relationship between the left superior frontal gyrus [peak MNI coordinates = -14, +12, +58] and left putamen [peak MNI coordinates = -28, +11, -04] functional connectivity (*X*) and delayed episodic memory (*Y*) among participants with MCI. For MCI participants with lower levels of left putamen tau (**blue**), delayed episodic memory increased as functional connectivity between the left superior frontal gyrus and left putamen increased. However, delayed episodic memory decreased for individuals with higher levels of left putamen tau (**red**) as functional connectivity between the left superior frontal gyrus and left putamen increased.

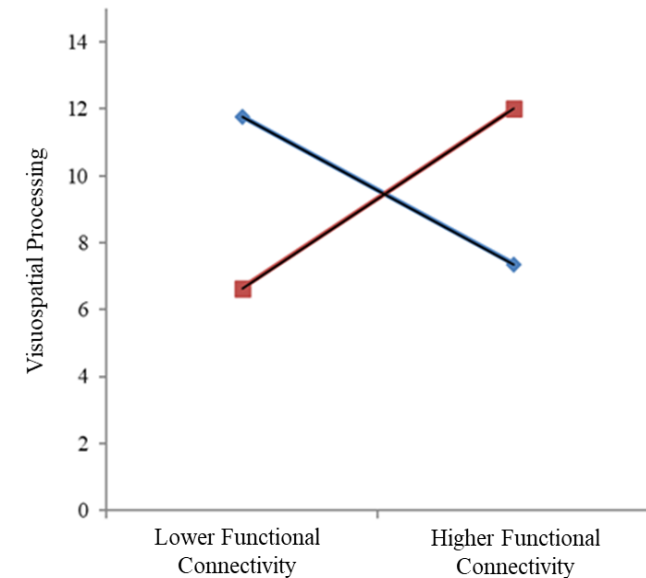
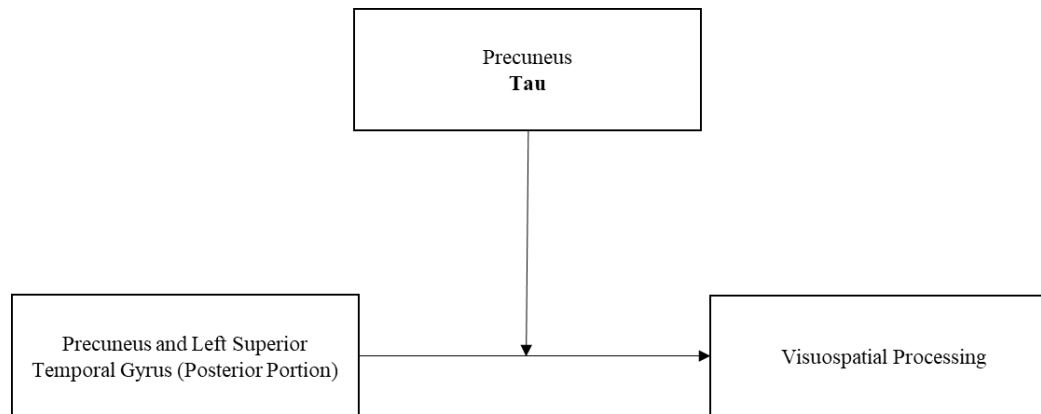


Figure 6.6l. Simple moderation model and interaction plot

Note: *Left*: Among mild cognitive impairment (MCI) participants, **precuneus tau load** was found to moderate (*M*) the relationship between precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity (*X*) and visuospatial processing (*Y*).

Right: An interaction plot showing the moderating effect of **precuneus tau load** (*M*) on the relationship between precuneus and left superior temporal gyrus (posterior portion) [peak MNI coordinates = -42, -12, -06] functional connectivity (*X*) and visuospatial processing (*Y*) among participants with MCI. For MCI participants with lower precuneus tau (**blue**), visuospatial processing decreased as functional connectivity between the precuneus and left superior temporal gyrus increased. However, for individuals with higher levels of precuneus tau (**red**), visuospatial processing increased as functional connectivity between the precuneus and left superior temporal gyrus (posterior portion) increased.

Table 6.2. Summary of Results: CU Participants

Functional Connection	Decreased / Increased Functional Connectivity	Moderator (A β / Tau)	Cognitive Domain	R ²	F	p-value	Survived Multiple Test Correction?
CU > DAT							
		A β					
Precuneus and Left Insula	Functional connectivity is higher among CU	Left Insula	Executive Function	.042	5.57	.020	×
		Tau					
Precuneus and Right Precentral	functional connectivity is higher among DAT	Precuneus	Visuospatial Processing	.050	7.00	.009	×
Precuneus and Right Precentral	Functional connectivity is higher among DAT	Right Precentral	Visuospatial Processing	.050	7.57	.007	×
Precuneus and Left Precentral	Functional connectivity is higher among CU	Precuneus	Visuospatial Processing	.030	4.04	.047	×

Notes. Functional connectivity = functional connectivity; CU = cognitively unimpaired; DAT = dementia due to Alzheimer's disease. Bold = survived multiple corrections. Red = evidence of reduced functional connectivity (CU functional connectivity > DAT functional connectivity); blue = increased functional connectivity (CU functional connectivity < DAT functional connectivity).

Table 6.3. Summary of Results: MCI Participants

Functional Connection	Decreased / Increased Functional Connectivity	Moderator (A β / Tau)	Cognitive Domain	R^2	F	p -value	Survived Multiple Test Correction?
MCI > DAT							
		A β					
Left Superior Frontal Gyrus and Left Putamen	Functional connectivity is higher among MCI	Left Superior Frontal Gyrus	Delayed Episodic Memory	.074	4.26	.045	✗
Left Superior Frontal Gyrus and Left Putamen	Functional connectivity is higher among MCI	Left Putamen	Delayed Episodic Memory	.099	5.72	.021	✗
Precuneus and Left Superior Temporal Gyrus (Posterior Portion)	Functional connectivity is higher among MCI	Precuneus	Visuospatial Processing	.107	5.86	.020	✗
Precuneus and Left Superior Temporal Gyrus (Posterior Portion)	Functional connectivity is higher among MCI	Left Superior Temporal Gyrus	Visuospatial Processing	.111	6.37	.015	✗
		Tau					
Precuneus and Left Precentral Gyrus	Functional connectivity is higher among AD	Precuneus	Executive Function	.360	8.44	.004	✗

Left Superior Frontal Gyrus and Left Putamen	Functional connectivity is higher among MCI	Left Superior Frontal Gyrus	Executive Function	.163	11.14	.002	×
Left Superior Frontal Gyrus and Left Putamen	Functional connectivity is higher among MCI	Left Putamen	Delayed Episodic Memory	.169	9.433	.004	×
Precuneus and Left Superior Temporal Gyrus (Posterior Portion)	Functional connectivity is higher among MCI	Precuneus	Visuospatial Processing	.076	4.32	.043	×

Notes. Functional connectivity = functional connectivity; MCI = mild cognitive impairment; DAT = dementia due to Alzheimer's disease. Bold = survived multiple corrections. **Red** = evidence of decreased functional connectivity (MCI functional connectivity > DAT functional connectivity); **blue** = increased functional connectivity (MCI functional connectivity < DAT functional connectivity).

6.5 Discussion

6.5.1 A β vs Tau as Modifiers of the Relationships Between Functional Connectivity and Multidomain Cognitive Performance

In both CU and MCI groups, regional tau pathology, compared to regional A β burden, was found to modify a greater number of relationships between functional connectivity and multidomain cognitive performance. No significant results were observed among DAT participants, and the most important effects were observed among MCI participants.

These findings suggest that regional tau pathology may have a more prominent role in moderating the relationships between specific functional connections and cognitive performance, particularly at the MCI stage. The brain often attempts to adapt to growing pathology at this intermediate stage. However, by the AD stage, advanced biological processing of AD may limit the impact of tau. It is important to note that the absence of significant findings in the DAT group could be partly attributable to the limited sample size.

The significant findings in the MCI group align with recent research. Sadeghi et al. (2024) observed that, among MCI participants, important relationships existed between functional connectivity (in this instance, the Default Mode network) and levels of tau and negative correlations between Default Mode network functional connectivity and levels of tau and phosphorylated tau, but not A β levels. Furthermore, work by Schoonhoven et al. (2023) results suggest that in addition to structural connections, functional connectivity (measured via magnetoencephalography) was found to play a significant role in tau spread and that measuring for changes in neural communication patterns may be more important during earlier stages of disease progression, e.g., preclinical AD and MCI (Schoonhoven et al., 2023).

6.5.2 Direction Patterns of Effects

Among CU participants, four significant interactions were observed: one involving A β and three involving tau. In cases with lower levels of regional A β or tau, functional connectivity increased,

associated with higher cognitive performance. Conversely, for those with higher levels of regional A β or tau, functional connectivity decreased and was linked to poorer cognitive performance.

However, among MCI participants, across seven out of eight significant interactions (four out of eight = A β , three out of eight = tau), among those with lower levels of regional A β / tau, functional connectivity was found to decrease, and this was associated with lower cognitive performance. Conversely, the opposite effect was observed among those with higher regional A β / tau levels. The remaining significant interaction (one out of eight) demonstrated a reversed effect (like that of CU) in that functional connectivity increased among those with lower regional A β / tau levels, which was associated with higher cognitive performance. However, the opposite effect was observed among those with higher regional A β / tau levels.

Firstly, among CU participants with lower regional A β / tau, increased functional connectivity might facilitate effective neural communication and enhance cognitive performance. However, for CU participants with higher levels of regional A β / tau, such increased functional connectivity patterns may not translate to cognitive benefits due to the underlying effects of higher pathology burden (e.g., neurodegenerative processes) having an overwhelming impact and mitigating any potential benefits. This could point towards a threshold effect, whereby functional connectivity becomes beneficial but only below a certain A β / tau level, where the spread of pathology surpasses it.

However, for MCI participants, these relationships were reversed for most (seven out of eight) significant relationships. Whereby only among MCI participants with higher regional A β / tau load higher levels of functional connectivity were associated with higher cognitive performance. Whereas, among those with lower regional A β / tau load, higher levels of functional connectivity were associated with lower cognitive performance.

Higher functional connectivity might indicate recruiting compensatory mechanisms among MCI participants with higher A β / tau load. These individuals may rely on increased functional connectivity to maintain cognitive performance despite the higher levels of underlying pathology. Conversely, for MCI participants with lower A β / tau load, increased functional connectivity could suggest the

recruitment of less efficient or redundant neural pathways as the brain struggles to adapt to emerging cognitive challenges, leading to lower cognitive performance.

6.5.3 Cognitive Domains Most Affected

Among CU participants, the resulting modifying effects of A β affected executive function, and tau exclusively affected the relationships between functional connectivity and visuospatial processing. The cognitive domains affected among MCI participants were more varied: the relationships between functional connectivity and visuospatial processing were affected three out of eight times, delayed memory = three out of eight times, and executive function two out of eight times.

Together, this may suggest that visuospatial processing may be one of the first cognitive domains affected by AD-related pathology and is supported by Begde et al. (2024), who found reduced visual processing speed to be significantly associated with future dementia.

6.6 Conclusions

These findings emphasise the differential impact of regional tau and A β pathology on functional connectivity and cognitive performance across the AD continuum. While no significant modifying effects were observed in participants with DAT, the results suggest that tau pathology may play a more substantial role than regional A β in modifying functional connectivity and cognitive performance, particularly among MCI participants.

The contrasting patterns of effects in CU and MCI participants highlight the dynamic nature of functional connectivity changes between disease stages. Among CU participants, increased functional connectivity in the presence of lower tau or A β levels may indicate beneficial neural communication. However, increased connectivity does not translate to cognitive benefits in those with higher pathology, possibly due to the overwhelming disease burden. In contrast, MCI participants with higher pathology seem to recruit compensatory connectivity to maintain cognitive function, while those with lower pathology might exhibit less efficient neural adaptation.

Furthermore, the modifying effects of A β and tau pathology on functional connectivity varied by cognitive domain. The early vulnerability of visuospatial processing to AD-related pathology among CU participants, particularly tau, may point towards this specific cognitive domain being a key marker for early detection and intervention. The broader range of affected domains (visuospatial, delayed memory, and executive function) among MCI participants may suggest a more extensive and varied cognitive decline within this cohort.

In conclusion, these results provide evidence for the importance of early-stage interventions targeting tau pathology and functional connectivity changes, particularly among individuals at the MCI stage.

**Chapter 7: Network-Level Functional Connectivity Within and
Between the Medial Temporal Lobe and Default Mode Network:
Specific Patterns Based on Amyloid Status**

7.1 Abstract

Background and Purpose: Changes in functional connectivity within the MTL and Default Mode network across AD stages are influenced by and, in turn, influence cortical A β and regional tau burden. While the role of functional connectivity in AD progression is well-established, its interaction with A β and its impact on regional tau deposition remain less explored.

Methods: I analysed CU participants from the OASIS-3 AV1451 cohort ($n = 287$), categorised into A β - ($n = 193$) and A β + ($n = 94$) groups based on A β -PET for cross-sectional analyses. PCA of functional connectivity identified two components: one reflecting MTL-functional connectivity and the other reflecting Default Mode network-functional connectivity. These components were correlated with regional tau deposition across Braak stages 1 to 6. A β status-specific robust regressions assessed the relationship between functional connectivity and tau burden.

Results: In A β - participants, lower “MTL Integration Axis” functional connectivity (PC1) was associated with higher tau levels in the left entorhinal cortex. In A β + participants, lower “MTL Integration Axis” functional connectivity correlated with elevated tau levels in the Default Mode network’s left lateral parietal cortex, MTL’s right parahippocampal cortex, and Braak stages 3 to 6 brain regions.

Conclusions: Decreased functional connectivity was associated with increased regional tau burden, showing A β status-specific effects. Enhancing MTL functional connectivity could be a therapeutic strategy for future AD clinical interventions.

7.2 Background

The MTL is comprised of crucial structures like the hippocampus, entorhinal cortex, and parahippocampal cortex, all of which are essential for memory formation, spatial information processing, and navigation (Squire et al., 2004). The Default Mode network, first described by Raichle et al. (2001), includes brain regions such as the medial prefrontal cortex, posterior cingulate cortex, precuneus, and inferior parietal lobule (Raichle et al., 2001). These regions exhibit synchronised activity during rest and are involved in introspective processes such as self-referential thinking, daydreaming, mind wandering, and recalling of personal experiences (Raichle et al., 2001; Greicius et al., 2003; Huntley et al., 2021).

Research suggests that elevated cerebral levels of A β and tau disrupt and impair neural communication and connectivity across multiple brain networks (Vogel et al., 2020; Ingala et al., 2021). This disruption underlines the complex link between molecular pathology and functional connectivity alterations in neurodegenerative diseases like AD. For instance, Giorgio et al. (2023) demonstrated that A β plaques, as assessed using PET, disrupt brain network interactions in CU older adults during task-based fMRI. Specifically, A β flips connections between MTL and Default Mode network from inhibitory to excitatory, leading to increased MTL activity and accelerating tau accumulation in the entorhinal cortex (Giorgio et al., 2023).

Despite advancements in brain imaging and the growing popularity of and focus on functional connectivity in the field of AD research, significant knowledge gaps remain in understanding how AD biomarkers like A β and tau influence local functional connectivity patterns within vulnerable brain networks and regions such as the MTL and Default Mode network. The differential effects of these neuropathological AD biomarkers on functional connectivity in CU older adults remain unclear and warrant further research. It is by gaining additional insight into these relationships and interactions that we gain a greater understanding of their potential role(s) in targeted treatment strategies to slow or prevent AD progression.

Hence, this study aimed to explore the relationships between functional connectivity within and between the MTL and Default Mode network and regional tau accumulation in these regions among CU participants while stratifying them based on sub-groups based on their cortical A β burden. Previous research has shown that functional connectivity can predict tau distribution among CN and AD participants (Franzmeier et al., 2019). Thus, we hypothesised that network-level functional connectivity would be associated with regional tau burden. Additionally, we anticipated that these relationships would differ between individuals with lower versus higher cortical A β burden as prior research has shown that elevated A β levels are linked to regional and global functional connectivity changes, even in individuals experiencing subjective cognitive decline (Li et al., 2021).

7.3 Methods

7.3.1 Study Design

For this Chapter, we chose to use OASIS-3 data (LaMontagne et al., 2019). As described in Chapter 3, T1-structural MRI, resting-state fMRI, A β -PET, and tau-PET data were downloaded from the OASIS-3 study cohort. This cross-sectional dataset includes participants who all underwent an ^{18}F -AV1451 (AV1451) tau-PET scan, allowing for the analysis of the relationships between functional connectivity and tau pathology at a single time point. All brain imaging scans included in this chapter occurred within six months of each other.

7.3.2 Study Participants

OASIS-3 CU participants ($n = 287$) with available T1-structural MRI, resting-state fMRI, A β -PET, AV1451 tau-PET data were further subdivided based on evidence of lower or elevated levels of cortical A β burden (A β - and A β +, respectively). Among these participants, 193 exhibited lower cortical A β burden (A β -; 67.25%), while 94 showed evidence of higher cortical A β burden (A β +/; 32.75%). Detailed inclusion and exclusion criteria for participant selection in the OASIS-3 study are provided by LaMontagne et al. (2019). See Chapter 3 for more details.

7.3.3 Pre-processing and Denoising

The same pre-processing and denoising pipelines as used with ADNI-3 data were adopted and run in CONN.

7.4 Data Analysis Summary

Participants were divided into two groups based on their A β status: A β ⁺ and A β ⁻. Large-scale functional connections within and between the MTL and the Default Mode network are analysed and subjected to PCA for dimensionality reduction. Robust linear regressions were then performed to examine the relationships between these PCs and regional tau levels, highlighting differences in these relationships between A β ⁺ and A β ⁻ groups.

A data analysis summary is illustrated in Figure 7.1.

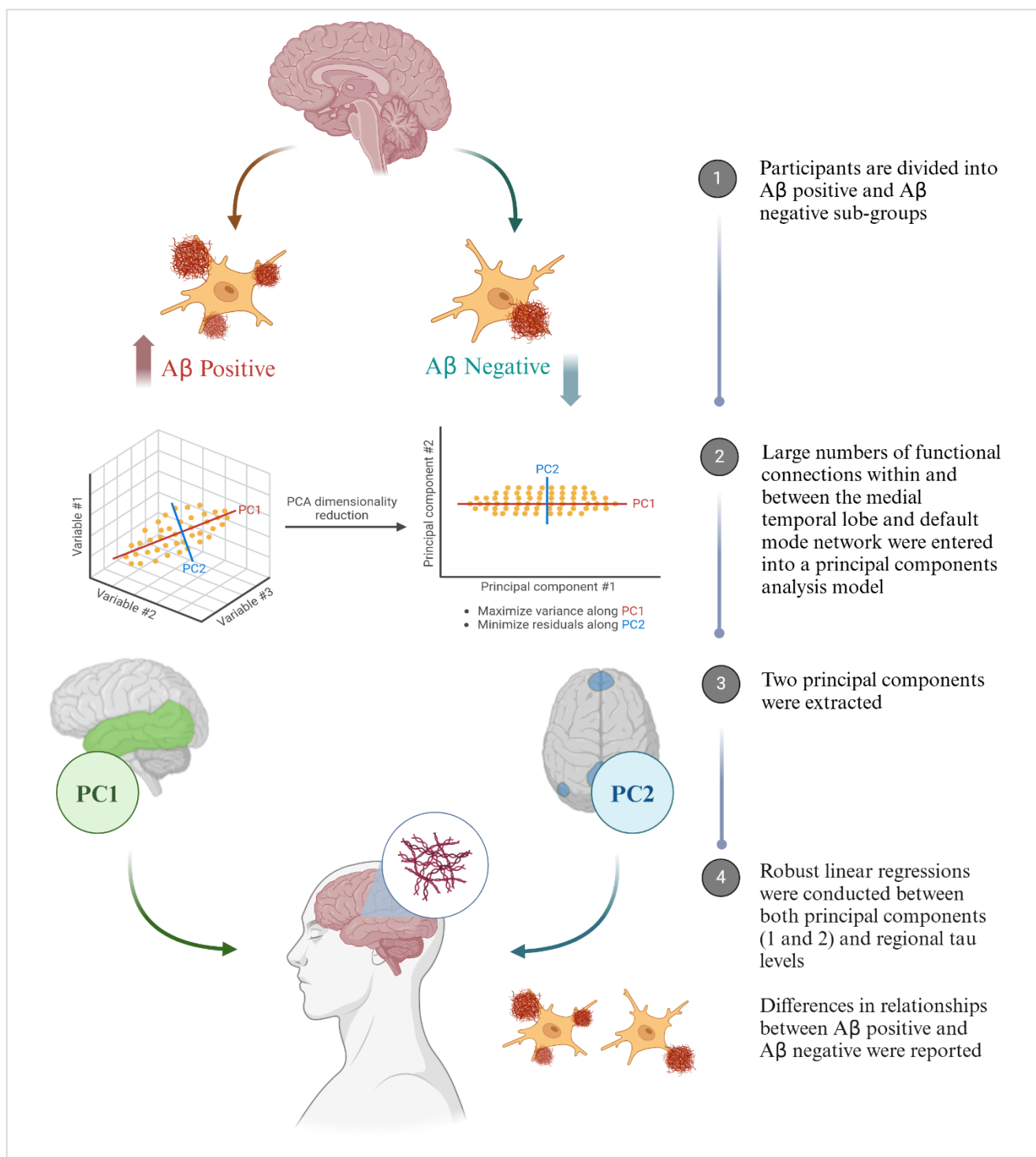


Figure 7.1. Conceptual illustration of analyses used in Chapter 7

Note: Aβ = amyloid-beta; PC1 / 2 = principal component 1 / 2. Created with Biorender.com.

7.5 Results

7.5.1 Demographics and Clinical Characteristics

In this study, participants with lower cortical A β burden (A β -) were, on average, younger ($M = 66.70$ years, $SD = 8.26$) compared to those with elevated A β burden (A β +; $M = 72.10$ years, $SD = 6.63$). The distribution of males and females was similar across the entire sample (males = 41.90% [$n = 122$] and females = 58.10% [$n = 169$]) but differed notably when stratified by A β status. Specifically, the highest proportion of participants was female A β - (38.70% [$n = 111$]), whereas the lowest proportion was male A β + (13.20%, $n = 38$).

Additionally, the mean TBV_{adjusted} values were equivalent for both A β - and A β + participants. However, A β + participants exhibited higher regional tau values and tau burden across all Braak stages.

Table 7.1. provides a more detailed overview of demographic and clinical characteristics, including stratification by A β status.

7.5.2 Braak Staging

Among the 193 A β - participants, 132 (68.39%) were classified as “Braak stage 0”; 35 (18.13%) as “Braak stage 1”; eight (4.15%) as “Braak stage 2”. No participants were classified as “Braak stage 3” or “Braak stage 4”. However, 18 (9.33%) participants were found to demonstrate evidence of atypical tau spread, e.g., showing overlap between multiple Braak stages and not fulfilling the criteria to be defined as a single stage (Figure 7.2.). Participants with overlapping criteria for various stages may suggest non-linear or atypical tau spread (see also Vogel et al., 2021).

In the A β + group of 94 participants, 30 (31.91%) were classified as “Braak stage 0”; 18 (19.15%) as “Braak stage 1”; 23 (24.47%) as “Braak stage 2”; three (3.19%) as “Braak stage 3”; five (5.32%) as “Braak stage 4”. 15 (15.96%) participants were found to demonstrate evidence of atypical tau spread (Figure 7.2.).

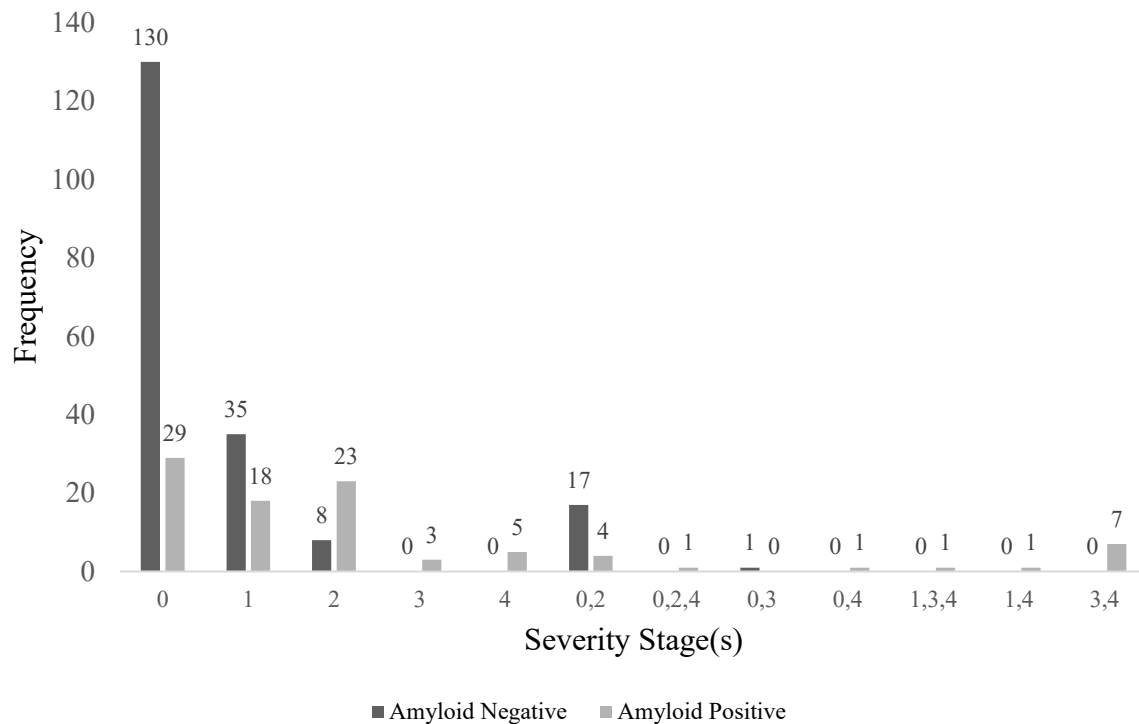


Figure 7.2. Frequency count for participants in each Braak stage: Stratified by A β status

Note: A β = amyloid-beta.

Chen et al.'s 2021 criteria categorised participants: 0 = Braak stages 1 / 2 standardised uptake value ratio (SUVR) < 1.129; 1 = Braak stages 1 / 2 SUVR between 1.129 and 1.307; 2 = Braak stages 3 / 4 SUVR between 1.308 and 1.523; 3 = Braak stages 3 / 4 SUVR between 1.524 and 1.873; and 4 = Braak stages 5 / 6 SUVR > 1.874. Braak stage regions by Braak and Braak (1991).

The latter seven categories demonstrate overlap across multiple severity stages, e.g., “Braak stages 0 and 2” = Braak stages 1 / 2 SUVR < 1.129 but Braak stages 3 / 4 SUVR between 1.308 and 1.523.

Table 7.1. Demographic and Clinical Characteristics of A β - and A β + Participants

Variable	Whole Sample	Aβ Status	
		Aβ-	Aβ+
		(<i>n</i> = 287)	(<i>n</i> = 193; 67.25%)
Demographics			
Age			
(M <i>SD</i>)	68.50 (8.16)	66.70 (8.26)	72.10 (6.63)
Sex (%)			
Males	122 (41.90)	82 (28.69)	38 (13.20)
Females	169 (58.10)	111 (38.70)	56 (19.50)
Years of Education			
(<i>M</i> <i>SD</i>)	148 / 287 (51.57)	111 / 148 (75.00)	37 / 148 (25.00)
	16.32 (2.29)	16.30 (2.26)	16.41 (2.41)
APOE			
APOE Carrier Status (%)			
Non-Carriers	88 / 146 (60.27)	77 / 146 (52.74)	11 / 146 (7.53)
Carriers	58 / 146 (39.73)	33 / 146 (22.60)	25 / 146 (17.12)
Brain Outcomes			
Structural MRI			
TBV _{adjusted} * (mm ³)			
(M <i>SD</i>)	1.50e ⁺⁶ (181697)	1.50e ⁺⁶ (178413)	1.50e ⁺⁶ (187501)
Tau-PET			
MTL, Left Entorhinal			
Cortex** (SUVr)	1.12 (.38)	.99 (.21)**	1.39 (.51)
(M <i>SD</i>)			

MTL, Right Entorhinal

<i>Cortex</i> (SUVr)	1.14 (.38)	1.02 (.26)	1.38 (.48)
(M <i>SD</i>)			

MTL, Left Hippocampus

(SUVr)	1.33 (.24)	1.28 (.22)	1.45 (.23)
(M <i>SD</i>)			

MTL, Right Hippocampus

(SUVr)	1.32 (.23)	1.26 (.21)	1.44 (.22)
(M <i>SD</i>)			

MTL, Left Parahippocampal

<i>Cortex</i> (SUVr)	1.06 (.25)	.99 (.16)	1.21 (.33)
(M <i>SD</i>)			

MTL, Right

<i>Parahippocampal Cortex</i>	1.05 (.26)	.98 (.18)	1.19 (.32)**
** (SUVr)			
(M <i>SD</i>)			

MTL, Left Amygdala (SUVr)

(M <i>SD</i>)	1.25 (.38)	1.12 (.19)	1.52 (.50)

MTL, Right Amygdala

(SUVr)	1.27 (.40)	1.13 (.19)	1.57 (.54)
(M <i>SD</i>)			

Default Mode Network,

<i>Medial Prefrontal Cortex</i>	1.05 (.26)	.99 (.17)	1.16 (.37)
(SUVr)			
(M <i>SD</i>)			

Default Mode Network,

Posterior Cingulate Cortex	1.37 (.31)	1.30 (.16)	1.51 (.45)
(SUVr)			
(M SD)			

Default Mode Network, Left

Lateral Parietal Cortex	1.39 (.49)	1.26 (.18)	1.65 (.75)
(SUVr)			
(M SD)			

Default Mode Network, Right

Lateral Parietal Cortex	1.39 (.46)	1.27 (.16)	1.63 (.71)
(SUVr)			
(M SD)			

Braak Stages 1-2 Tau (SUVr)

(M SD)	1.13 (.37)	1.01 (.21)	1.38 (.47)

Braak Stages 3-4 Tau**

(SUVr)	1.23 (.19)	1.18 (.12)	1.35 (.24)**
(M SD)			

Braak Stages 5-6 Tau**

(SUVr)	1.34 (.37)	1.24 (.12)	1.56 (.57)**
(M SD)			

Notes: A β = amyloid status (- / +); M = mean; SD = standard deviation; SUVr = standardised uptake value ratio; TBV_{adjusted} = an adjusted measure of total brain volume; MTL = medial temporal lobe.

- Braak stages 1-2: entorhinal cortex,
- Braak stages 3-4: amygdala, Accumbens area, hippocampus, insula, medial orbitofrontal gyrus, lateral orbitofrontal, pars orbitalis, parahippocampal cortex, rostral anterior cingulate cortex, posterior cingulate cortex, caudal anterior cingulate cortex, isthmus cingulate cortex,

-
- Braak stages 5-6: banks of the superior temporal sulcus, middle temporal gyrus, caudal middle frontal gyrus, fusiform gyrus, inferior parietal gyrus, inferior temporal gyrus, lateral occipital gyrus, supramarginal gyrus, and precuneus.

* $TBV_{adjusted}$ was calculated using prior work by Voevodskaya et al. (2014).

** Functional connectivity was associated with tau levels within this region.

7.5.3 ROI-to-ROI Analysis

One hundred and sixty functional connections (of a possible 182) were statistically significant across 10 clusters ($p < .05$). These clusters were derived using optimal lead ordering for hierarchical clustering based on the region of interest-to-region of interest anatomical proximity (see Bar-Joseph et al., 2001). The functional connections within each of the 10 clusters were averaged, forming 10 values (one per cluster) for each participant. This was conducted to reduce data dimensionality, minimise noise, and simplify the subsequent PCA model whilst attempting to maintain biologically plausible components. The loadings of each cluster, as revealed by region of interest-to-region of interest analysis, were as follows: Cluster 1: “Within-functional connectivity” (left and right portions of the posterior parahippocampal cortex); Cluster 2: “Within-functional connectivity” (across Default Mode network sub-regions); Cluster 3: “Within-functional connectivity” (across MTL sub-regions); Cluster 4: “Within-functional connectivity” (posterior parahippocampal cortex to other MTL sub-regions); Cluster 5: “Within-functional connectivity” (left and right portions of the entorhinal cortex); Cluster 6: “Between-functional connectivity” (MTL to Default Mode network sub-regions [1]); Cluster 7: “Between-functional connectivity” (MTL to Default Mode network sub-regions [2]); Cluster 8: “Within-functional connectivity” (entorhinal cortex to other MTL sub-regions); Cluster 9: “Within-functional connectivity” (entorhinal cortex to portions of the posterior parahippocampal cortex); and Cluster 10: “Between-functional connectivity” (entorhinal cortex to sub-regions of the Default Mode network). Of the 160 total statistically significant connections ($p < .05$), 86 were “Within-MTL”, 12 were “within-Default Mode network”, and 62 were “Between MTL-Default Mode network”.

7.5.4 PCA

PCA was conducted using cluster averages 1 to 10 and revealed a two-factor solution (see Table 7.2.), which was validated visually using the scree plot. PC1 comprised Clusters 3, 4, 5, 8, and 9, while PC2 included Clusters 2, 4, 6, 7, and 10. Cluster 4 loaded significantly on both PC1 and PC2. Conversely, Cluster 1 did not load onto any PC until PC4. Given that the eigenvalue for a four-factor solution was < 1 , Cluster 1 was excluded from subsequent analyses.

PC1 had a sum of squares value of 2.25 and explained 22.50% of the total variance, whilst PC2 had a sum of squares value of 2.15 and explained 21.50% of the total variance (with a cumulative variance of 44.00%). Inter-correlations between PC1 and PC2 were .23.

Bartlett's test of sphericity was significant: $X^2(45) = 598, p < .001$, and Kaiser-Meyer-Olkin measure of sampling adequacy (overall) = .67 and ranged from .44 (Cluster 1) to .83 (Cluster 2), supporting PCA to be conducted with a two-factor solution. PC1 and PC2 were labelled based on the following rationales:

- PC1 - "MTL Integration Axis": This label denotes the integration of various connections within the MTL.
- PC2 - "Default Mode Network Integration Axis": similarly, this label conveys the integration of connections within the Default Mode network, as well as its interactions with other brain regions, such as the MTL. It highlights the coordinated activity within the Default Mode network and related structures.

The Shapiro-Wilk test was used to determine whether the distributions of PC1 and PC2 followed a normal distribution. PC1 was not normally distributed ($W = .98, p = .001$) but PC2 was normally distributed ($W = .99, p = .050$).

Table 7.2. Component Loadings for Cluster Averages 1 to 10

	Principal Component		
	PC1	PC2	Uniqueness
<i>CI*</i>	-	-	.97
<i>C2</i>	-	.61	.50
<i>C3</i>	.61	-	.49
<i>C4</i>	<u>.56</u>	<u>.33</u>	.49
<i>C5</i>	.56	-	.71
<i>C6</i>	-	.85	.30
<i>C7</i>	-	.83	.32
<i>C8</i>	.84	-	.33
<i>C9</i>	.63	-	.61
<i>C10</i>	-	.33	.89
PC			
	C3, C4, C5, C8, and C9	C2, C4, C6, C7, and C10	
Summaries			

Notes. Component loadings for cluster averages 1 to 10. PC = principal component; C = cluster.

Underlined = cross-loadings across PCs 1 and 2.

- **C1:** “Within-functional connectivity” (left and right portions of the posterior parahippocampal cortex),
- **C2:** “Within-functional connectivity” (across Default Mode network sub-regions),
- **C3:** “Within-functional connectivity” (across medial temporal lobe [MTL] sub-regions),
- **C4:** “Within-functional connectivity” (posterior parahippocampal cortex to other MTL sub-regions),
- **C5:** “Within-functional connectivity” (left and right portions of the entorhinal cortex),
- **C6:** “Between-functional connectivity” (MTL to Default Mode network sub-regions [1]),
- **C7:** “Between-functional connectivity” (MTL to Default Mode network sub-regions [2]),
- **C8:** “Within-functional connectivity” (entorhinal cortex to other MTL sub-regions),

-
- **C9:** “Within-functional connectivity” (entorhinal cortex to portions of the posterior parahippocampal cortex); and
 - **C10:** “Between-functional connectivity” (entorhinal cortex to sub-regions of the Default Mode network).

*C1 did not load onto any PC until PC4, but the eigenvalue was < 1 .

7.5.5 Spearman's Rank Correlations Between Functional Connectivity and Tau Burden

7.5.5.1 In CU A β - Individuals

One correlation was statistically significant between “MTL Integration Axis” functional connectivity and MTL, left entorhinal cortex, $\rho = -.15$, $p = .038$. No significant correlations were observed between the other variables. Table 7.3. shows correlation strengths between “MTL Integration Axis” functional connectivity and “Default Mode network Integration Axis” functional connectivity and tau burden of brain regions corresponding to Braak stages 1 to 6 among A β - participants.

7.5.5.2 In CU A β + Individuals

Four relationships were statistically significant: “MTL Integration Axis” functional connectivity and Default Mode network, left lateral parietal cortex tau, $\rho = -.21$, $p = .047$; and “MTL Integration Axis” functional connectivity and MTL, right parahippocampal cortex tau, $\rho = -.22$, $p = .032$. Furthermore, “MTL Integration Axis” functional connectivity and Braak stages 3 to 4 tau regions, $\rho = -.30$, $p = .004$; and “MTL Integration Axis” functional connectivity and Braak stages 5 to 6 tau regions, $\rho = -.22$, $p = .033$. Table 7.4. shows correlation strengths between “MTL Integration Axis” functional connectivity and “Default Mode network Integration Axis” functional connectivity and tau burden of brain regions corresponding to Braak stages 1 to 6 among A β + participants.

Table 7.3. Correlation Matrix Showing Relationships Between Functional Connectivity and Braak Stage Tau Burden Among Aβ-

		“MTL Integration Axis” Functional Connectivity	“Default Mode Network Integration Axis” Functional Connectivity	Braak (1 to 2)	Braak (3 to 4)	Braak (5 to 6)
“MTL Integration Axis” Functional Connectivity	<i>df</i> <i>p-value</i>					
“Default Mode Network Integration Axis” Functional Connectivity	<i>df</i> <i>p-value</i>	.18** 191 .013				
Braak (1 to 2)	<i>df</i> <i>p-value</i>	.00 191 .984	-.14 191 .058			
Braak (3 to 4)	<i>df</i> <i>p-value</i>	-.09 191 .637	.03 191 .636	.26*** 191 <.001		
Braak (5 to 6)	<i>df</i> <i>p-value</i>	-.03 191 .637	.01 191 .872	.25*** 191 <.001	.67*** 191 <.001	

Notes. * $p < .05$, ** $p < .01$, *** $p < .001$. Aβ- = amyloid-beta negative participants; MTL = medial temporal lobe; *df* = degrees of freedom. Warmer colours denote the strength of positive relationships; cooler colours denote the strength of negative relationships. Braak stages 1 to 2: entorhinal cortex, Braak stages 3 to 4: amygdala, Accumbens area, hippocampus, insula, medial orbitofrontal gyrus, lateral orbitofrontal, pars orbitalis, parahippocampal cortex, rostral anterior cingulate cortex, posterior cingulate cortex, caudal anterior cingulate cortex, isthmus cingulate cortex, Braak stages 5 to 6: banks of the superior temporal sulcus, middle temporal gyrus, caudal middle frontal gyrus, fusiform gyrus, inferior parietal gyrus, inferior temporal gyrus, lateral occipital gyrus, supramarginal gyrus, and precuneus.

Table 7.4. Correlation Matrix Showing Relationships Between Functional Connectivity and Braak Stage Tau Burden Among Aβ+

		“MTL Integration Axis” Functional Connectivity	“Default Mode Network Integration Axis” Functional Connectivity	Braak (1 to 2)	Braak (3 to 4)	Braak (5 to 6)
“MTL Integration Axis” Functional Connectivity	<i>df</i> <i>p-value</i>					
“Default Mode Network Integration Axis” Functional Connectivity	<i>df</i> <i>p-value</i>	.77*** 92 <.001				
Braak (1 to 2)	<i>df</i> <i>p-value</i>	-.11 92 .279	.02 92 .840			
Braak (3 to 4)	<i>df</i> <i>p-value</i>	-.30** 92 .004	-.17 92 .095	.61*** 92 <.001		
Braak (5 to 6)	<i>df</i> <i>p-value</i>	-.22* 92 .033	-.17 92 .105	.37*** 92 <.001	.78*** 92 <.001	

Note. * $p < .05$, ** $p < .01$, *** $p < .001$. Aβ- = amyloid-beta negative participants; MTL = medial temporal lobe; *df* = degrees of freedom. Warmer colours denote the strength of positive relationships; cooler colours denote the strength of negative relationships. Braak stages 1 to 2: entorhinal cortex, Braak stages 3 to 4: amygdala, Accumbens area, hippocampus, insula, medial orbitofrontal gyrus, lateral orbitofrontal, pars orbitalis, parahippocampal cortex, rostral anterior cingulate cortex, posterior cingulate cortex, caudal anterior cingulate cortex, isthmus cingulate cortex, Braak stages 5 to 6: banks of the superior temporal sulcus, middle temporal gyrus, caudal middle frontal gyrus, fusiform gyrus, inferior parietal gyrus, inferior temporal gyrus, lateral occipital gyrus, supramarginal gyrus, and precuneus.

7.5.6 Robust Regression Models: Functional Connectivity Predicting Tau Burden

A visual summary of A β status-specific results can be found in Figure 7.3.

7.5.6.1 In CU A β - Individuals

One robust regression was statistically significant among A β - participants:

- a. **“MTL Integration Axis” functional connectivity predicting MTL, left entorhinal cortex tau:** the model fit statistics revealed an R^2 value of .03 (explaining 2.50% of the variance in MTL, left entorhinal cortex tau), ($F[1, 191] = 4.82, p = .029$). Analysis of variance (ANOVA) tests showed a significant model effect (sum of squares = .21, $F[1, 191] = 4.82, p = .029$), with “MTL Integration Axis” functional connectivity specifically contributing significantly (sum of squares=.21, $F[1, 191] = 6.10, p = .014$). The parameter estimates indicated that the intercept was .99 (standard error [SE] = .02, $T[191] = 66.53, p < .001$), while “MTL Integration Axis” functional connectivity had a negative estimate of -.03 ($SE = .01, T[191] = -2.47, p = .014$), suggesting that as “MTL Integration Axis” functional connectivity increased, MTL, left entorhinal cortex tau decreased.

7.5.6.2 In CU A β + Individuals

Four robust linear regressions were run for A β + participants (two for specific regional burden of tau and two across various Braak stages):

- a. **“MTL Integration Axis” functional connectivity predicting Default Mode network, left lateral parietal cortex tau:** the model fit statistics indicated an R^2 of .05, meaning the model accounted for 5.00% of the variance in Default Mode network, left lateral parietal cortex tau ($F[1, 92] = 4.85, p = .030$). ANOVA tests showed a significant effect for the model (sum of squares = 2.62, $F[1, 92] = 4.85, p = .030$, with “MTL Integration Axis” functional connectivity specifically contributing significantly (sum of squares = 2.62, $F[1, 92] = 4.61, p = .034$). Parameter estimates revealed the intercept at 1.65 ($SE = .08, T[92] = 21.61, p < .001$) and “MTL Integration Axis” functional connectivity with a negative estimate of -.17 ($SE = .08, T[92] = -$

2.15, $p = .034$). Higher “MTL Integration Axis” functional connectivity values are associated with lower values of Default Mode network, left lateral parietal cortex tau.

- b. **“MTL Integration Axis” functional connectivity predicting MTL, right parahippocampal cortex tau:** the model fit statistics indicated an R^2 of .07, meaning the model accounted for 7.40% of the variance in MTL, right parahippocampal cortex tau ($F[1, 92] = 7.33, p = .008$). ANOVA tests showed a significant effect for the model (sum of squares = .71, $F[1, 92] = 7.33, p = .008$), with “MTL Integration Axis” functional connectivity specifically contributing significantly (sum of squares = .71, $F[1, 92] = 7.23, p = .009$). Parameter estimates revealed the intercept at 1.19 ($SE = .032, T[92] = 36.94, p < .001$) and “MTL Integration Axis” functional connectivity with a negative estimate of -.09 ($SE = .03, T[92] = -2.69, p = .009$), suggesting that higher values of “MTL Integration Axis” functional connectivity are associated with lower values of MTL, right parahippocampal cortex tau.
- c. **“MTL Integration Axis” functional connectivity predicting Braak stages 3 to 4 tau:** model fit statistics indicated an R^2 of .09, meaning the model accounted for 8.80% of the variance in Braak stages 3 to 4 tau ($F[1, 92] = 8.85, p = .004$). ANOVA tests showed a significant effect for the model (sum of squares = .46, $F[1, 92] = 8.85, p = .004$) and specifically for “MTL Integration Axis” functional connectivity (sum of squares = .46, $F[1, 92] = 5.34, p = .023$). Parameter estimates revealed the intercept at 1.35 ($SE = .02, T[92] = 56.74, p < .001$) and “MTL Integration Axis” functional connectivity with a negative estimate of -.07 ($SE = .03, T[92] = -2.31, p = .023$), suggesting that higher values of “MTL Integration Axis” functional connectivity are associated with lower values of Braak stages 3 to 4.
- d. **“MTL Integration Axis” functional connectivity predicting Braak stages 5 to 6 tau:** model fit statistics indicated an R^2 of .048, meaning the model accounted for 4.80% of the variance in Braak stages 5 to 6 tau ($F[1, 92] = 4.68, p = .033$). ANOVA tests showed a significant effect

for the model (sum of squares = 1.47, $F[1, 92] = 4.68$, $p = .033$) and specifically for “MTL Integration Axis” functional connectivity (sum of squares = 1.47, $F[1, 92] = 4.64$, $p = .034$). Parameter estimates revealed the intercept at 1.56 ($SE = .06$, $T[92] = 26.65$, $p < .001$) and “MTL Integration Axis” functional connectivity with a negative estimate of -.13 ($SE = .06$, $T[92] = -2.16$, $p = .034$). Higher values of “MTL Integration Axis” functional connectivity are associated with lower Braak stages 5 to 6 tau values.

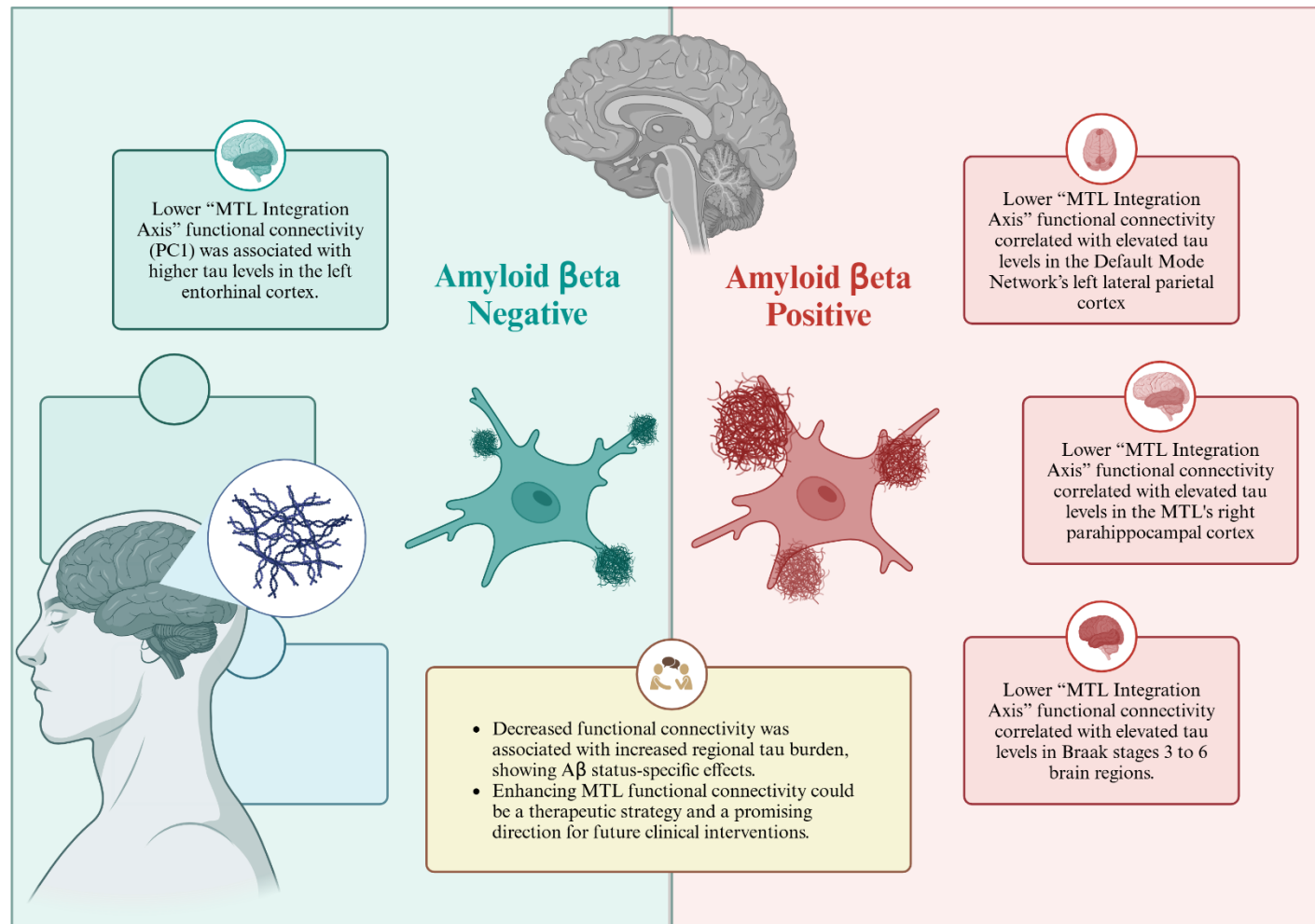


Figure 7.3. A visual summary of A β status-specific results

Note: A β = amyloid-beta. MTL = Medial Temporal Lobe; PC1 = principal component 1. Created with Biorender.com.

7.6 Discussion

This chapter investigated the relationships between MTL and Default Mode network functional connectivity and regional tau accumulation in older adults, stratified by A β - and A β + status. The findings revealed that lower “MTL Integration Axis” functional connectivity was associated with greater regional tau burden, and these effects were more pronounced among participants with elevated cortical A β deposition. This highlights the potential role of cortical A β in modulating tau distribution and altering network functional dynamics.

7.6.1 Differential Impact of “MTL Integration Axis” Functional Connectivity and “Default Mode Network Integration Axis” Functional Connectivity on Tau Pathology Between A β Statuses

“MTL Integration Axis” functional connectivity (PC1) was positively correlated with “Default Mode network Integration Axis” functional connectivity (PC2) in both A β - and A β + groups, with a significantly stronger correlation observed among those with elevated A β burden. This stronger correlation among A β + might reflect A β -related hyperactivity, as higher levels of A β deposition are linked to increased activity within the MTL (Pasquini et al., 2019), potentially amplifying MTL to Default Mode network functional connectivity, contributing to network disruption and tau accumulation.

The influence of “MTL Integration Axis” functional connectivity on tau pathology demonstrated differences between A β status groups. Specifically, “MTL Integration Axis” functional connectivity was identified as a negative predictor of MTL, left entorhinal cortex tau levels, suggesting that, among those with lower levels of A β pathology (A β - [as measured by PET]), higher “MTL Integration Axis” functional connectivity was associated with reduced tau burden within the left entorhinal cortex. However, the statistical significance of this relationship was accompanied by a modest R^2 value, indicating that additional factors may also play a role in shaping this association.

Compared to A β - participants, those with elevated cortical A β levels exhibited more spatially varied and statistically significant relationships between “MTL Integration Axis” functional connectivity and regional tau burden. Although the R^2 values were relatively modest, ranging from 4.80 - 8.80%, these findings suggest that “MTL Integration Axis” functional connectivity is more substantial in predicting regional tau distribution in participants with elevated cortical A β levels. AD is a highly heterogeneous condition, so elucidating additional sources of variance in functional connectivity-tau relationships may help uncover the pathophysiological processes occurring during the early stages of AD among older adults.

Relevant to these results is research by Roemer-Cassiano et al. (2025) who demonstrated that A β deposition induces neuronal hyperactivity and enhances functional connectivity, potentially facilitating the propagation of tau pathology. Their results showed that elevated A β levels were associated with increased functional connectivity between tau epicentres and distal brain regions, a phenomenon observed in early AD stages and replicated across independent cohorts. Moreover, heightened functional connectivity correlated with an accelerated rate of tau accumulation, supporting the model of transneuronal tau dissemination. Notably, A β -driven functional connectivity alterations mediated the association between A β burden and tau progression, implicating hyperconnectivity as a mechanistic driver of AD pathogenesis. These findings suggest that targeting A β -induced neuronal hyperactivity and connectivity alterations may represent a viable therapeutic strategy to mitigate tau-related neurodegeneration in AD.

Functional connectivity along the “MTL Integration Axis” correlated with tau pathology in several regions. In contrast, functional connectivity along the “Default Mode Network Integration Axis” did not show significant correlations with tau pathology within any of the areas included. In AD, tau pathology tends to follow a stereotypical pattern, starting in the MTL and spreading to other cortical regions, as described by Braak staging (Braak & Braak, 1991). In our sample of CU older adults, the lack of significant relationships between “Default Mode Network Integration Axis” functional connectivity and regional tau might reflect an earlier stage of tau spread. These relationships may become more apparent in the later stages of the disease.

7.6.2 Potential Mechanisms

In this cross-sectional study, increased functional connectivity and elevated cortical A β burden (measured by PET) may point towards early neurodegeneration. Increasing tau pathology is associated with the disruption of functional connectivity (Nabizadeh, 2024). As tau pathology increases, it exacerbates the loss of functional connectivity, which is critical for cognitive processes (Berron et al., 2021). Our results suggest a particular vulnerability of those with elevated cortical A β burden, despite no evidence of cognitive impairment, in moderating the relationships between functional connectivity and tau. Higher cortical A β appears to disrupt these relationships within clinically pertinent brain regions. Namely, the relationships between “MTL Integration Axis” functional connectivity and tau within the Default Mode network, left lateral parietal cortex; MTL, right parahippocampal cortex; and Braak stages 3 to 6 brain regions. We predict that early neurodegenerative process, as evidenced by the association between lower functional connectivity and higher tau pathology, is indicative of the impact of cortical A β on brain regions associated with cognition, even before evidence of cognitive impairment is apparent.

Higher “MTL Integration Axis” functional connectivity may also indicate stronger network integrity or adaptive neuroplasticity, potentially mitigating the neurotoxic effects of tau accumulation. This interpretation is supported by previous research emphasising the crucial role of neuroplasticity in brain health. Synaptic plasticity - the ability of synapses to strengthen or weaken over time in response to activity changes - is essential for maintaining cognitive functions and promoting recovery after neural damage (Bassi et al., 2019). However, this plasticity diminishes with age, particularly in brain regions critical for learning and memory, such as the hippocampus (Wong et al., 2021).

Because of this, individuals with higher “MTL Integration Axis” functional connectivity may demonstrate cognitive resilience, maintaining cognitive functions despite tau pathology. We propose that enhancing functional connectivity and promoting neuroplasticity could serve as strategies to potentially mitigate cognitive decline in older adults at risk of AD.

One such strategy is utilising transcranial magnetic stimulation, a non-invasive neuromodulation technique that modulates brain activity via a series of magnetic pulses to specific brain areas (Weiler et al., 2019). These pulses can influence neuronal excitability and synaptic plasticity (Weiler et al., 2019). Transcranial magnetic stimulation (or similar imaging modalities) may enhance functional connectivity between these areas by targeting regions outlined in this study. This enhancement may aid in counteracting the functional connectivity and tau pathology changes observed during the early stages of AD.

Another important concept closely related to neuroplasticity is cognitive reserve. Cognitive reserve is the brain's capacity to utilise its accumulated lifetime resources, such as education, intellectual engagement, and social activities, to mitigate the negative effects of brain pathology and maintain its levels of cognitive function (Stern, 2009). Recent research identified education as a significant determinant of cognitive and brain resilience against tau pathology (Bocancea et al., 2023). In the context of the results of this current study, higher “MTL Integration Axis” functional connectivity may reflect stronger network integrity. Therefore, it is hypothesised that these individuals exhibiting higher network integrity also possess greater cognitive reserve. By accounting for individual differences in cognitive reserve, we may enhance our findings' explanatory power and applicability within general linear models predicting the relationships between functional connectivity and tau pathology.

Education has often been used as a rough proxy of cognitive reserve (Tucker & Stern, 2011). Surprisingly, A β ⁺ participants had slightly higher educational attainment compared to A β ⁻. However, this difference was slight, and data describing both years of education and A β status were only available for 51.57% of the total sample (with only 37 being A β ⁺). Hence, to further explore this hypothesis, larger samples describing educational attainment and other measures of cognitive reserve (e.g., occupational complexity, engagement in cognitive and social activities, and other measures) are needed.

Prior research by Giorgio et al. (2023), using task-based fMRI and multimodal PET imaging, revealed that A β deposition disrupts the excitatory-inhibitory balance in the Default Mode network, resulting in hyperexcitation within the Default Mode network itself. This hyperexcitation subsequently

increased activity within the MTL, and elevated MTL activity, driven by Default Mode network hyperexcitation, predicted accelerated tau accumulation in the entorhinal cortex. Our findings suggest that disturbances induced by A β in Default Mode network function may initiate a cascade of changes within the brain and contribute to the progression of tau pathology in AD. Our study aligns with Giorgio et al. (2023) in demonstrating A β 's impact on functional connectivity. However, unlike Giorgio et al. (2023), our study found that a higher A β burden alters the relationship between MTL functional connectivity and regional tau accumulation within the MTL rather than the Default Mode network. These differences may stem from methodological choices, such as task-based vs. resting-state fMRI. Furthermore, the complex interplay between A β , tau, and functional connectivity may exhibit non-linear effects, leading to differences in study outcomes.

7.6.3 Clinical Implications and Potential Biomarkers

The results from this study may point towards clinical interventions aimed at increasing “MTL Integration Axis” functional connectivity to potentially modify tau pathology progression, even at the earliest stages of AD. Gaining further insight into the relationships between functional connectivity and tau progression may aid in informing disease models and therapeutic strategies.

In this cross-sectional study, “MTL Integration Axis” functional connectivity demonstrated significant relationships between regional tau burden across multiple regions, particularly when cortical A β were elevated. Therefore, functional connectivity could serve as a potential biomarker for early detection or progression of AD, particularly in the context of cortical A β pathology.

Stam et al. (2023) explored the relationship between excitation-inhibition balance, which involves the dynamic equilibrium of neural signals, and functional connectivity. Previous research by Schoonhoven et al. (2022) characterised AD by alterations in functional connectivity across different frequency bands - specifically, a decrease in functional connectivity in higher frequency bands and an increase in functional connectivity in lower frequency bands.

This understanding aligns with prior research utilising AD animal models. For example, Tombini et al. (2021) demonstrated that network hyperexcitability was associated with abnormal protein accumulation, and this may further exacerbate their deposition.

The finding that most CU participants were in early Braak stages (0 or 1), but some were progressing to later stages (Braak stages 2 to 4) highlights the importance of early detection and ongoing clinical monitoring. Furthermore, I found atypical tau accumulation patterns that do not align with traditional Braak staging. This may suggest that AD might not always follow a predictable path (see also Vogel et al., 2021). This points towards a need for more flexible and comprehensive assessment tools that consider individual variability in regional pathological accumulation and further explore the mechanisms underlying this atypicality.

7.7 Conclusions

This chapter emphasises the significance of local (network-level) functional connectivity relationships with regional tau deposition, with these relationships being contingent on cortical A β status. Specifically, among participants with lower A β levels, lower “MTL Integration Axis” functional connectivity was associated with higher tau levels in the left entorhinal cortex. Whereas, among participants with higher A β levels, lower “MTL Integration Axis” functional connectivity correlated with elevated tau levels in the Default Mode network’s left lateral parietal cortex, MTL’s right parahippocampal cortex, and Braak stages 3 to 6 brain regions.

Our findings suggest that enhancing functional connectivity of the MTL could serve as a potential therapeutic target and offer a promising avenue for future clinical interventions to mitigate tau-related neurodegeneration in AD, particularly among those with elevated cortical A β .

Chapter 8: Overall Discussion and Conclusions

8.1 Key Results and Summary

This thesis integrated two primary methodological frameworks: “data-driven” and “hypothesis-driven” approaches. These frameworks guided the organisation and interpretation of our findings. The key findings are also summarised in Figure 8.1.

8.1.1 Data-driven Approaches

The first set of results presented in Chapter 4 introduced the utility of “data-driven” methodologies by employing whole-brain ROI-to-ROI analyses to examine functional connectivity differences across three participant groups: CU, MCI, and DAT. The findings revealed significant differences in functional connectivity patterns when comparing CU and DAT and MCI and DAT participants. However, no significant differences were observed between CU and MCI participants. This prompted a set of follow-up analyses whereby CU and MCI participants were subdivided further into groups based on whether they possessed lower or higher levels of cortical A β burden (A β - and A β +). This sub-grouping aimed to uncover subtle functional connectivity patterns that might be masked in broader group comparisons.

Next, Multivariate Pattern Analysis (Chapter 5) was employed to investigate group-level differences in functional connectivity further. Consistent with results from Chapter 4, no statistically significant functional connectivity differences were observed between CU and MCI participants. Yet, significant differences emerged when comparing CU and DAT participants and MCI and DAT participants. This was followed by conducting ROI-to-voxel (across the whole brain) seed-based connectivity analysis, targeting specific “seeds” identified by Multivariate Pattern Analysis.

Interestingly, differences in functional connectivity were observed between CU and MCI participants when they were further stratified by A β status (A β - and A β +). Even so, these differences were only observed at the network-level point of spatial resolution.

Lastly, seven graph theory measures were applied to characterise group-level functional connectivity differences comprehensively. These measures provided a more nuanced understanding of the

topological properties of the brain's functional networks, enriching the interpretation of functional connectivity pattern differences observed between groups.

In Chapter 6, regional tau, more so than regional A β , was identified as a key modifier of the relationships between functional connectivity and multidomain cognitive performance. This effect was most pronounced among MCI participants, compared to CU. Regional A β and tau did not have a measurable influence on any relationships between functional connectivity and multidomain cognitive performance among DAT participants.

8.1.2 Hypothesis-Driven Approaches

Chapter 7 adopted a “hypothesis-driven” framework to investigate group-level functional connectivity differences within and between the MTL and Default Mode network among a sample of CU older adults. These participants were stratified into sub-groups based on their cortical A β burden (A β - and A β +), providing a nuanced perspective on functional connectivity patterns.

Among CU A β - participants, reduced “MTL Integration Axis” functional connectivity (PC1) was associated with higher tau levels, specifically in the left entorhinal cortex. By contrast, in CU A β + participants, lower “MTL Integration Axis” functional connectivity was linked to elevated regional tau levels across a broader range of regions: the Default Mode network's left lateral parietal cortex, the MTL's right parahippocampal cortex, and Braak stages 3 to 6 brain regions.

The next sections will explore deeper into these findings by placing them within the wider context of available scientific literature, discussing the potential clinical applications of our results, evaluating the overall strengths and limitations of this project, and offering recommendations for future research.

8.2 Group-Level Differences in Functional Connectivity

This project's initial functional connectivity analysis (Chapter 4) employed a whole-brain ROI-to-ROI approach with TFCE to examine group-level differences across CU, MCI, and DAT participants. When comparing CU and DAT participants, 20 spatial clusters of functional connectivity were revealed, with the right inferior frontal gyrus (pars triangularis) emerging as the most frequently implicated brain region within these clusters. Next, when examining MCI vs. DAT participants, 12 spatial clusters were identified, with the right inferior temporal gyrus (temporooccipital part) being the most frequently cited region. Notably, no significant results were found between CU and MCI participants.

Given the larger 'gap' between the stages involved, the greatest number of clusters derived from when computing the group-level contrast - CU vs. DAT - was expected. However, the absence of functional connectivity differences between CU and MCI was unexpected, especially considering the observed differences in the other group comparisons. This prompted supplementary analyses stratifying CU and MCI participants into A β sub-groups: CU A β -, CU A β +, MCI A β -, and MCI A β +. This stratification aimed to identify subtle differences masked in the initial group-level analysis.

Graph theory metrics were first employed in Chapter 4 to characterise group-level differences in functional connectivity. Betweenness centrality (the proportion of times a node lies on the shortest path between other nodes) exhibited significant differences across all three group comparisons (CU vs. MCI, CU vs. DAT, and MCI vs. DAT). Differences in average path length were also observed, but only between CU and DAT and MCI and DAT group comparisons. Therefore, betweenness centrality was a common feature between all three group comparisons, whereas average path length differences were specific to CU vs DAT and MCI vs DAT comparisons.

Surprisingly, betweenness centrality is underutilised in whole-brain level functional connectivity studies. For instance, Weiler et al. (2018) used this graph theory measure (alongside several others) to explore and estimate network efficiency and its relationship with cognitive reserve. They found that, compared to controls, the amnesic-MCI group presented increased and decreased betweenness centrality in several brain networks. They predicted that those with higher cognitive reserve may possess

more effective means to cope with accumulating AD pathology via more efficient networks (Weiler et al., 2018). Similarly, Tu et al. (2024) found that hubs with high global functional connectivity were found to be particularly vulnerable to reductions in functional connectivity among older adults with autosomal dominant AD, occurring approximately eight years before the onset of symptoms and these disruptions in hub connectivity were shown to increase in severity during clinical progression. The researchers also posited that “hub disruption was primarily tied to regional differences in global [functional] connectivity and sequentially followed changes observed in A β PET cortical markers” (Tu et al., 2024).

Changes in network properties may highlight a breakdown of network organisation between AD stages, suggesting the need for more graph theory metrics to be adopted to test its utility as a possible biomarker.

In Chapter 5, group-level differences in functional connectivity – as assessed using Multivariate Pattern Analysis – were identified in two out of three group comparisons: CU vs. DAT and MCI vs. DAT participants. Consistent with findings in Chapter 4, no significant differences were observed between CU and MCI participants.

In the comparison between the CU and DAT groups, the Multivariate Pattern Analysis identified the left thalamus and precuneus as key brain regions that significantly contributed to the variance in functional connectivity between the two groups. I then adopted a seed-based connectivity approach to explore these findings further, using the left thalamus and precuneus as seed regions.

This follow-up revealed distinct functional connectivity patterns between CU and DAT and MCI and DAT participants:

- Higher functional connectivity was observed in CU participants (compared to DAT) between the left thalamus [peak MNI coordinates = -06, -08, 00] and the right inferior temporal gyrus [peak MNI coordinates = +56, +02, -35].
- Lower functional connectivity was observed in CU participants (compared to DAT) between the left thalamus [peak MNI coordinates = -06, -08, 00] and (1) the right inferior frontal gyrus (pars triangularis) [peak MNI coordinates = +46, +32, +28] and (2) between the left thalamus

[peak MNI coordinates = -06, -08, 00] and the right postcentral gyrus [peak MNI coordinates = +52, -12, +30].

- Lower functional connectivity was observed in MCI participants (compared to DAT) between the left thalamus [peak MNI coordinates = -07, -26, +02] and the left Crus II [peak MNI coordinates = -38, -75, -35].

These findings emphasise the nuanced role of thalamic functional connectivity in differentiating CU and DAT, and MCI and DAT participants.

The thalamus has been aptly described as the “gateway of consciousness” (Crick & Koch, 2003). This multifaceted region supports various functions, including somatosensory processing (Klostermann et al., 2009) and sensory integration (Wolff et al., 2021). Beyond its sensory-related role, the thalamus is also involved in supporting cognition (Saalmann & Kastner, 2015), language (Hebb & Ojemann, 2013), and consciousness (experiencing one’s environment and internal state; Redinbaugh et al., 2020). Moreover, a review by Wolff et al. (2021) concluded that the thalamus is a vital bridge between perception and cognition (Wolff et al., 2021). Propagating its essential role in integrating the dynamic flow of information is paramount for coherent thought, awareness, and action.

Given these considerations, an important question emerges: could individual differences in functional connectivity patterns, particularly among brain regions supporting sensory processing, partially account for the observed heterogeneity of functional connectivity between earlier and later AD stages? Such differences have been called a “functional fingerprint” or signature (Finn et al., 2015).

This concept is exemplified in a study by Wisch et al. (2020), which developed a global resting-state functional connectivity signature based on intra-network connections to distinguish between CU and AD participants. Surprisingly, the Default Mode and Memory networks played less prominent roles in this global signature than the Sensorimotor networks (Wisch et al., 2020). This unexpected finding emphasises the importance of sensory regions in AD-related functional connectivity changes.

Notably, regions comprising the Sensorimotor network have exhibited functional connectivity with the thalamus (Kawabata et al., 2021), suggesting a possible link between sensory processing disruptions during AD development. These findings are particularly relevant to this thesis, as the results from

Chapters 5 and 6 support the idea that brain regions involved in sensory processing, such as the thalamus, may play a critical role in AD development.

Moreover, it has been reported that thalamic-sensorimotor functional connectivity disturbances may be implicated in inappropriate sensory information processing among both bipolar disorder and schizophrenia patients, potentially explaining some visual-related symptoms in both of these disorders, e.g., hallucinations (Long et al., 2020).

There appears to be a bidirectional relationship between changes in the visual system and brain regions associated with sensory processing. For instance, a large-scale meta-analysis comprising data from over 75,000 participants found that visual impairment may serve as a potential risk factor for future cognitive decline and dementia (Cao et al., 2023). Similar findings have been reported in relation to hearing loss in a review by Ralli et al. (2019), highlighting its association with an increased risk of AD.

Despite these findings, the exact mechanisms underlying the links between sensory impairment and cognitive decline still remain unclear. For hearing loss, the “sensory deprivation theory” suggests that sensory degradation in those with hearing impairment may result in loss of input to the corresponding cortical regions that may, in turn, give rise to functional and structural deficits within and between the auditory and cognitive systems (Tarawneh et al., 2022), and shrinkage of the optic tract was also found among patients with thalamic stroke (Ye et al., 2022).

Next, the precuneus showed bidirectional (increased and decreased) functional connectivity patterns.

- Higher functional connectivity among CU participants was evident compared to DAT participants between the precuneus and the left precentral gyrus [peak MNI coordinates = -52, -02, +20], left middle occipital gyrus [peak MNI coordinates = -38, -92, -08], and left insula [peak MNI coordinates = -29, +10, -16].
- Lower functional connectivity among CU participants (compared to DAT) between the precuneus and the right precentral gyrus [peak MNI coordinates = +32, -08, +48].

The precuneus is a well-studied brain region due to its critical role as a connectivity hub within large-scale brain networks (Aghakhanyan et al., 2018). Like the thalamus, the precuneus supports multiple

functional processes, including (but not limited to) one's sense of self, consciousness, visuospatial processing, executive function, and memory; according to a review by Cavanna and Trimble (2006). It is also known for its high metabolic demand, with glucose consumption rates approximately 35% higher than in other areas of the cerebral cortex (Gusnard & Raichle, 2001), which may make it vulnerable to A β aggregation (Aghakhanyan et al., 2018).

Supporting this idea, Hansson & Gouras (2016) observed that the precuneus exhibited hypermetabolism during early preclinical AD stages when A β deposition begins. They hypothesised that this hyperactivity, induced by A β accumulation, may create a state of heightened vulnerability that predisposes the region to future neurodegeneration.

Interestingly, Koch et al. (2022) showed that 24 weeks of repetitive transcranial magnetic stimulation targeting the precuneus may slow cognitive and functional decline among those with mild – to – moderate AD. It has also been shown that in participants with either MCI or mild-AD dementia, improvements in “the Alzheimer’s Disease Assessment Scale–Cognitive Subscale” scores were significantly correlated with increases of the hippocampus–to–precuneus functional connectivity following repetitive transcranial magnetic stimulation, in as little as four weeks (Jung et al., 2024).

The thalamus and precuneus serve multiple purposes (often with functional overlap) and may be implicated in AD development. Moreover, these regions are highly structurally connected via white matter tracts that physically interconnect these areas, with changes to structural and functional connectivity possibly indicative of dynamic shifts in cortical hub regions among brain regions involved in consciousness (Cunningham et al., 2017).

Sub-regions of the frontal gyri were extracted as seed regions to compare functional connectivity between MCI and DAT participants. Significant functional connectivity differences were observed in this group contrast, unlike the left thalamus and precuneus. The involvement of the frontal gyri in the MCI vs. DAT group contrast may be specific for MCI participants. This could suggest that impairments in frontal functional connectivity become more pronounced as individuals transition from normal ageing to the early stages of AD.

In summary, the results from this project suggest that both the left thalamus and the precuneus appear to be important regions that account for the greatest amount of functional connectivity variance across group comparisons within the AD spectrum. In contrast, sub-regions of the frontal gyri showed significant differences in functional connectivity only when comparing MCI and DAT participants.

While my Multivariate Pattern Analysis approach demonstrated that the left thalamus, precuneus, and left. Right portions of the superior frontal gyrus explain the most variance of functional connectivity between CU and DAT and MCI and DAT participants; no significant differences in functional connectivity were observed between CU and MCI participants (a) when using a whole brain ROI-to-ROI and (b) in Multivariate Pattern Analysis. This suggests that functional connectivity differences between these groups are absent at this spatial scale. It is also possible that these groups exhibit considerable inter-subject variability or heterogeneity, as functional connectivity differences are more likely to be statistically significant in regions with low variability, such as primary sensory and motor cortices, compared to areas with high variability (Mueller et al., 2013).

8.3 A β and Tau as Moderators of The Relationships Between Functional Connectivity and Multidomain Cognitive Performance

8.3.1 Cognitive Domains Most Affected By A β and Tau

An interesting finding from my research, outlined in Chapter 6, was that among CU participants, regional A β and tau modified several relationships between functional connectivity and cognition, but only in the cognitive domain of visuospatial processing. In contrast, among MCI patients, regional A β and tau were found to modify a broader range of relationships between functional connectivity and cognition, including visuospatial processing, delayed memory, and executive function. This suggests that the relationships between functional connectivity and visuospatial processing performance might be more vulnerable to the effects of early A β and tau burden during the early stages of AD. This is supported by research by Plaza-Rosales et al. (2023). Using electroencephalography and eye movement tracking during a spatial navigation task, they found that early AD participants, compared to controls, exhibited impaired spatial learning, reduced targeted visual exploration, decreased occipital brain activity, and weaker beta-band connectivity in the prefrontal cortex (Plaza-Rosales et al., 2023). These findings highlight the potential of combining electroencephalography with visuospatial tasks to aid in identifying early markers for AD and providing a promising avenue for early diagnosis (Plaza-Rosales et al., 2023).

Prior research by Berente et al. (2022) investigated visuospatial functions and brain networks in a sample of older adults with amnesic MCI. Several important findings emerged from their study: visuospatial function was the most impaired cognitive domain, lateral temporal cortical thinning was a hallmark among those with amnesic MCI, and group-level differences in functional connectivity present between various sub-connections of the ‘visuospatial’ network (Berente et al., 2022). They concluded that changes in the Visuospatial network in amnesic-MCI patients using resting-state fMRI may be a potential new biomarker for early detection of cognitive decline (Berente et al., 2022).

Additionally, a review by Derby et al. (2022) highlighted that despite those with MCI demonstrating impairments in visuospatial attentional processing and working memory, many studies focused

(sometimes exclusively) on assessing for memory impairment. Consequently, Derby and colleagues emphasised the need for more research to investigate the potentially bidirectional relationships of memory and attention influencing each other (Derby et al., 2022).

When investigating the role of regional A β and tau moderating the relationships between functional connectivity and multidomain cognitive performance in individuals with MCI, several cognitive domains were found to be affected. Specifically, A β moderated the relationships between various functional connections and delayed episodic memory and visuospatial processing. On the other hand, Tau moderated the relationships between various functional connections and delayed episodic memory, visuospatial processing, and executive function.

The moderating effects of tau, more so than A β , may reflect region-specific vulnerabilities associated with AD biomarkers. These changes could influence the relationships between functional connectivity and various cognitive domains across both CU and MCI stages, highlighting the differential impact of A β and tau on brain function in early AD.

8.4 A β Status Specific Differences in MTL-Default Mode Network Functional Connectivity Patterns

In Chapter 7, when adopting a “hypothesis-driven” approach, it was found that lower functional connectivity within the MTL was associated with higher regional tau burden. This effect was more pronounced across a wider range of MTL areas in individuals with higher cortical A β burden (A β +) compared to those with lower cortical A β burden (A β -). These findings suggest that, even at one of the earliest stages of AD, where no significant cognitive decline or deficits are evident, distinct functional connectivity patterns can emerge depending on cortical A β load. Specifically, lower functional within the MTL predicted higher regional tau burden (within the MTL) among those with higher cortical A β levels.

Another interesting finding was that among A β - participants, the correlation between Default Mode network functional connectivity and MTL functional connectivity was weaker than A β +. I hypothesise that the stronger correlation observed among the A β + group might reflect A β -related hyperactivity and network disruption, which could indicate early neurodegeneration. This disruption may be partially attributed to differences in A β burden contributing to these early differences in functional connectivity.

The findings in Chapter 7 collectively suggest a nuanced relationship between tau pathology and functional connectivity, where tau alone might not necessarily drive functional connectivity differences, but rather, its effects become more evident in the presence of higher levels of cortical A β (A β +. Reinforcing that A β might prime the brain for tau-related disruptions (Jacobs et al., 2018). The interdependence of A β and tau supports the hypothesis that A β accumulation might facilitate or amplify the detrimental effects of tau via brain network functional connectivity (Giorgio et al., 2023). My results further this by suggesting that these effects are more prominent in individuals with elevated cortical A β burden.

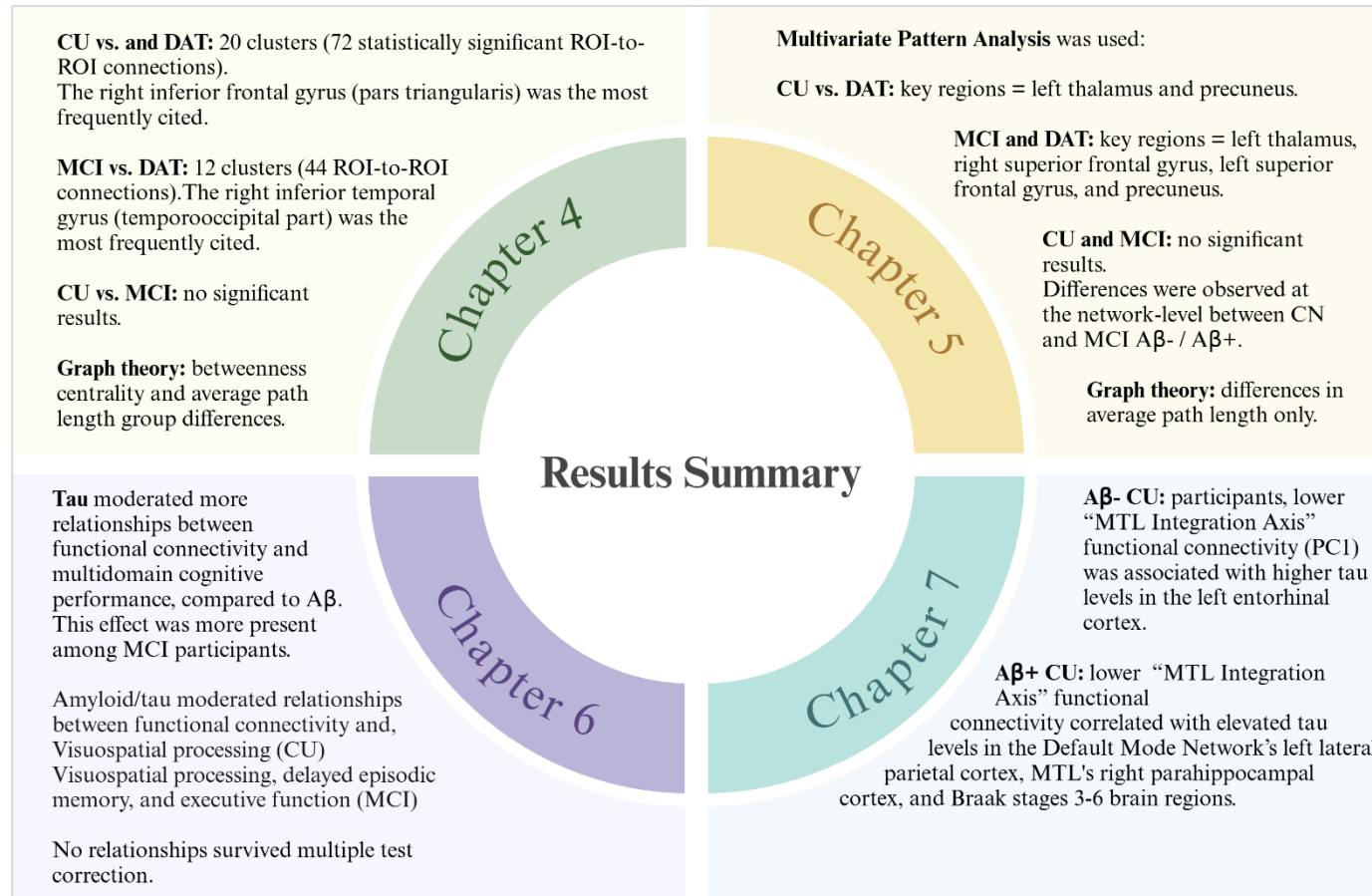


Figure 8.1. Thesis results summary

Note: Chapters 4 to 7. CU = cognitively unimpaired; MCI = Mild Cognitive Impairment; DAT = Dementia due to Alzheimer’s disease; ROI = Region of Interest;

Aβ = amyloid beta; MTL = medial temporal lobe.

8.5 Clinical Applications

Statistical analyses in Chapter 6 revealed that regional A β and tau levels moderated the relationships between various functional connections and multidomain cognitive performance. More of these relationships were observed among individuals with MCI compared to CU participants, and no significant relationships were found in those with DAT. This suggests that, even at earlier stages of AD, regional accumulation of both A β and tau can exert significant, localised effects on functional outcomes. Understanding the precise relationships between A β and tau accumulations in specific brain regions and their functional connectivity could provide crucial insights for targeted therapeutic approaches. This is further supported by findings in Chapter 7, where more relationships between regional tau and functional connectivity were evident within various sub-regions of the MTL rather than the Default Mode network. These relationships were more apparent among those with higher cortical A β . I hypothesise that the effectiveness of anti-A β and anti-tau medical interventions is greater before the spread of tau from the MTL to the neocortex. This ultimately reinforces the need for multimodal imaging methods (fMRI and PET) in precision medicine, allowing for more targeted and timely treatment and interventions.

Another potential clinical application stemming from the results of Chapter 6 could be the adoption of functional connectivity measures as outcome measures alongside cognitive performance. Especially as (a) functional connectivity is shown to demonstrate relationships with cognitive performance (Lin et al., 2018), and (b) the relationships between various functional connections and cognition appear to be significantly modified by the regional accumulation of AD biomarkers (particularly tau).

This chapter also observed an interesting phenomenon: a tendency for the direction of relationships to ‘flip’ between CU and MCI participants. This relationship shift could suggest that, as individuals transition from CU to MCI, certain physiological processes that initially serve a compensatory or adaptive function may alter their impact, becoming less beneficial (or even detrimental) between CU and MCI. One possible explanation for this effect could be that in the early stages of cognitive decline, the brain engages compensatory mechanisms to maintain cognitive function (as described in a review

by Bunzeck et al., 2024). In theory, while these processes may be advantageous and help sustain normal cognition in the face of emerging pathology, they may eventually reach a threshold where continued reliance on these compensatory mechanisms leads to inefficiency or exhaustion – resulting in these processes, once protective, becoming disadvantageous. This shift from possible compensation to possible dysfunction could reflect the brain's limited ability to sustain adaptive responses over time in the presence of AD biomarker accumulation (Stern et al., 2020). This phenomenon may also highlight the dynamic nature of brain plasticity and adaptability, further highlighting that interventions aimed at enhancing compensation might be beneficial during the early stages of cognitive decline but could become less effective (or even potentially harmful in terms of its effect on cognitive performance) as the disease progresses from CU to MCI (e.g., Thomas et al., 2019; Sha et al., 2022; Yu et al., 2024). However, it is important to note that the findings of Chapter 6 were insignificant after multiple test corrections were applied. Therefore, my aim for future research will be to explore this phenomenon further with more datasets and a less exploratory approach.

As mentioned, Chapter 7 identified lower MTL functional connectivity associated with higher regional tau burden, particularly among participants with elevated cortical A β burden (A β +). This finding suggests that enhancing MTL functional connectivity through neuromodulation techniques (e.g., transcranial magnetic stimulation, deep brain stimulation) may be a promising research area. The goal would be to reduce the regional tau burden within the MTL, especially during the early stages of AD. This is particularly relevant because the MTL is the primary set of brain regions where tau begins to spread to other brain areas (Braak & Braak, 1991).

In addition to neuromodulation, clinical trials testing the efficacy of disease-modifying treatments (anti-A β and anti-tau) could benefit from measuring potential changes in functional connectivity - with a particular focus on MTL sub-regions among CU older adults. This approach could provide added value and insights into how these treatments may influence network dynamics across brain regions implicated in early tau spread. Together, these points give further support to the concept of personalised medicine in AD and dementia research, as advocated by Arafah et al. (2023).

In addition, all participants included in Chapter 7 were CU. Finding differences in functional connectivity patterns at this early stage may be a means to identify high-risk, yet asymptomatic, older adults with functional connectivity signatures that may put them at risk of increased tau burden in the future.

Another, albeit unexpected, potential clinical application derived from the results of Chapter 7 is the identification of individuals with non-stereotypical tau spatial spread patterns. I identified a subset of participants who displayed ‘atypical’ tau patterns, deviating from the more typical location-specific accumulation associated with Braak staging (Braak & Braak, 1991). These irregular tau spatial patterns may represent an additional source of disease heterogeneity. Future studies could benefit from exploring this source of variability and assessing whether these differences are linked to distinct longitudinal cognitive and functional outcomes (e.g., by comparing relationships between those with “typical” vs “atypical” tau spatial patterns). Franzmeier et al. (2020) offer support for this approach. Their study found that a patient-centred tau spreading model using connectivity measures improved the assessment of tau accumulation rates compared to a Braak stage approach. Specifically, over time, the researchers found tau accumulation rates to correlate with functional connectivity strength to patient-specific tau epicentres (Franzmeier et al., 2020).

A summary of these proposed clinical applications can be found in Figure 8.2.

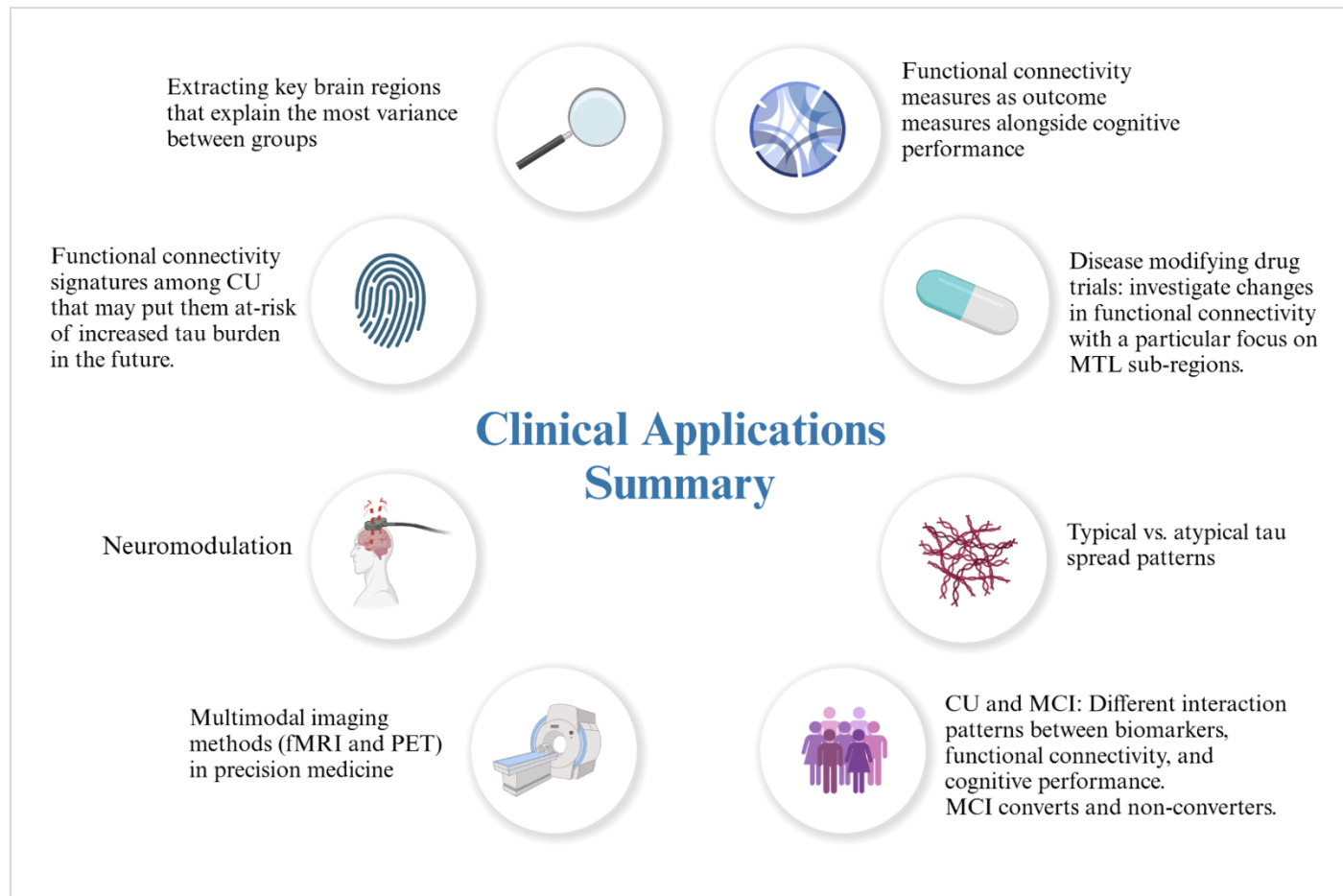


Figure 8.2. Summary of clinical applications based upon the results of this project

Note: CU = cognitively unimpaired; MCI = mild cognitive impairment; fMRI = functional magnetic resonance imaging; PET = positron emission tomography.

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8.6 Strengths and Limitations

8.6.1 Strengths

This project provides valuable insights into the relationships between functional connectivity (as measured using resting-state fMRI) and *in vivo* biomarkers of AD Pathology, specifically, A β and tau. One of the key strengths of this work is the inclusion of both “data-driven” and “hypothesis-driven” approaches, leveraging the advantages of both frameworks.

The data-driven approach reduces the potential bias associated with pre-selecting ROIs. This allows for functional connectivity patterns to emerge naturally from the data and ensures that the analyses remain unbiased. In contrast, the hypothesis-driven approach focuses on regions already known to be significantly affected by AD. A dual strategy provides complementary perspectives from both frameworks:

- Data-driven explorations (Chapters 4 to 6): These began with functional connectivity data, identifying broader clusters, regions, and networks that exhibited meaningful differences between groups.
- Hypothesis-driven analyses focused on predefined brain regions of interest, such as the MTL and the Default Mode network, which are critically implicated in AD development.

Combining both approaches provided a broad overview and targeted insights into the relationships between functional connectivity and AD neuropathology.

Secondly, this project used a diverse range of functional connectivity and statistical methods to encapsulate and characterise group-level differences in functional connectivity:

1. Whole-brain ROI-to-ROI analysis with TFCE (Chapter 4),
2. Multivariate Pattern Analysis with seed-based connectivity analysis (Chapter 5),
3. Multiple graph theory metrics (Chapters 4, 5, and 7), and
4. Network-level ROI-to-ROI analysis (Chapter 7).

Using multiple brain imaging and statistical methodologies is a significant strength of this project because it allowed for a more in-depth and nuanced investigation to understand group-level differences in functional connectivity between AD stages.

By adopting a multi-method approach to capture complex functional connectivity patterns using such high-dimensional data, we hope that results derived from our methodological choices will support future research trials and broaden our understanding of the complex relationships between functional connectivity and AD biomarkers.

Another strength of this project is the application of dimensionality reduction methods (Multivariate Pattern Analysis and PCA). Brain imaging is complex, high-dimensional data (Adams et al., 2019). Multivariate Pattern Analysis (Chapter 5) can detect subtle patterns of functional connectivity (in this project's case, between groups) compared to more traditional mass univariate approaches (Nieto-Castanon, 2022). Furthermore, PCA (Chapter 7) allowed us to ensure that I was focusing on PCs that capture the most variance across the MTL and Default Mode network.

In addition, measuring and including multiple cognitive domains into the moderation analysis models (Chapter 6) allowed us to uncover visuospatial processing (across both CU and MCI) and delayed episodic memory and executive function (MCI-specific) as potential outcomes of interest for future studies. However, our data-driven approach exponentially increased the number of hypotheses that required testing in this chapter (explained below under Limitations).

Lastly, ADNI-3 and OASIS-3 utilised (separate) standardised data acquisition protocols for structural MRI, resting-state fMRI, and ($A\beta$ and tau) PET data acquisition. By adopting a standardised approach, the data collected is consistent between participants, thus minimising sources of variability, e.g., across different equipment, imaging parameters, subject handling, etc. Furthermore, the importance of standardisation is why, for this thesis, I chose to use the same pre-processing, denoising, and quality control pipelines for ADNI-3 and OASIS-3, as I believe this helps mitigate discrepancies that might otherwise arise from using different data processing methods.

8.6.2 Limitations

One limitation of this study is its reliance on a cross-sectional design. This restricts the ability to study longitudinal trajectories and establish causal relationships.

A longitudinal element was not used in this project due to:

- ADNI-3's sample size falling exponentially when including additional time points and
- The University of Washington restricts OASIS-3's longitudinal data.

However, more longitudinal data of this nature will likely become more available in the future.

Although we certainly acknowledge the importance of longitudinal analyses, in studies of neurodegenerative diseases like AD, participants often begin with relatively stable physical health (Müller et al., 2021). However, as the study progresses, participants' physical health and ability to complete neuroimaging requirements tend to decline, leading to missing data and lower scan quality with each follow-up (Müller et al., 2021). This decline introduces variability in noise across participants, especially between patients and controls (Müller et al., 2021).

There was noticeable sample attrition in ADNI-3 (the number of participants with an available structural MRI, resting-state fMRI, and A β - and tau-PET scans decreased exponentially over time). As well as additional access limitations on OASIS-3 Tau (AV1451) longitudinal data.

Furthermore, MRI analysis significantly benefits from consistent data acquisition methods (Sharma & Saindane, 2020). In longitudinal studies, however, updates to scanner hardware and software and minor adjustments to acquisition protocols can introduce variability (Potvin et al., 2019). Consequently, this may complicate distinguishing between true longitudinal changes and artefacts (Potvin et al., 2019).

Another limitation of this project is its sample size, particularly the relatively small number of participants with DAT within the ADNI-3 dataset. A small sample size can reduce the statistical power of analyses, increasing the likelihood of type I errors and reducing confidence in detecting true group-level differences. This also has implications for internal validity (the accuracy of the findings; Kemper, 2017) and external validity (the generalisability of the findings; Findley et al., 2021).

Nonetheless, as argued by Indrayan and Mishra (2021), research should prioritise optimal study design, accurate measurements, robust analyses, and correct interpretation over sample size alone. Our research echoes this principle. From the beginning of this project, I prioritised standardisation across all stages of my research project, including the handling, processing, analysis, and reporting of data and research outcomes.

While these efforts enhance the validity and reliability of our results, some noise that significantly impacted the integrity of the results may still have remained. The BOLD signal is inherently noisy, and the underlying neuronal activity represents a small portion of the overall variance in signal (Bianciardi et al., 2009).

In Chapter 5, I did not identify significant differences in functional connectivity between CU and MCI participants until:

- CU and MCI participants were stratified by A β status and
- Functional connectivity models were amended to the network-level point of spatial resolution.

These observations highlight the potential influence of heterogeneity within the cohort. For example, MCI participants demonstrate significant levels of heterogeneity, a factor that is challenging to account for (Wang et al., 2023). One such solution may be the sub-categorisation of MCI into distinct sub-categories, e.g., into early- vs. late-MCI (Edmonds et al., 2019). Sub-categorisation may help delineate finer group differences. However, this potentially creates further problems with more cross-combinations between groups, requiring more hypotheses to test (which inflates the possibility of type I errors) and reducing the sample sizes for each cohort. There is also diagnostic ambiguity in determining where these participants are (early- or late-MCI) and no real standardisation for these diagnostic categories (Albert et al., 2011).

Another limitation in Chapter 6 concerns the inclusion of both CU A β ⁺ and CU A β ⁻ participants within a single diagnostic category when examining the moderating effects of amyloid and tau on the relationships between functional connectivity and multidomain cognitive performance. This approach was chosen for three reasons: (a) to provide a more ecologically valid representation of this

heterogeneous population. This is because the preclinical stage of AD includes both A β ⁺ and A β ⁻ individuals. (b) Preserving sample size is crucial for ensuring sufficient statistical power. Lastly, (c) including both A β ⁺ and A β ⁻ CU participants allows for investigating factors influencing resilience and susceptibility to cognitive decline by recognising that not all A β ⁺ CU participants will go on to progress to MCI or AD. This inclusive approach also mitigates the potential for inflating the number of hypotheses to be tested, which would arise from subgroup analyses. However, we acknowledge that individuals with higher cortical A β loads are more likely to progress to MCI or AD (Doraiswamy et al., 2014), and these participants could disproportionately contribute to the observed effects in this chapter. Future studies employing more focused, hypothesis-driven approaches may be warranted to investigate these relationships among CU participants further.

Although this project has revealed multiple relationships between AD biomarkers (A β and tau) with functional connectivity across the whole brain and network-level point of spatial resolution, the inherent high dimensionality of resting-state fMRI data to measure functionality connectivity, BOLD signal's inherent levels of noise, and hardware and physiological sources of variability, may cast doubt in whether functional connectivity could serve as a robust and reliable AD biomarker.

To support this is the concept of neurovascular coupling (the relationship between neural activity and blood flow; He et al., 2020). The underlying physiological processes of neurovascular coupling can vary across brain regions (Ekstrom, 2021). Deeper brain structures, like the hippocampus, demonstrate regional and frequency-wise differences (Ekstrom, 2021). Also, many individuals across the AD continuum have vascular pathology like cerebrovascular disease (Attems & Jellinger, 2014), which can independently disrupt blood flow and the resulting BOLD signal (Iadecola et al., 2023).

Advanced age has been linked to impairments in neurovascular coupling responses among otherwise healthy older adults (Lipcz et al., 2019). Neurovascular coupling and functional connectivity were reduced in MCI participants compared to CU, particularly in the left dorsolateral prefrontal cortex (Owens et al., 2024). This suggests that alterations in neurovascular coupling and functional connectivity are prominent features in individuals with MCI (Owens et al., 2024).

A further consideration in this project, particularly relevant to the analysis of high-dimensional neuroimaging data, concerns the challenges associated with multiple test corrections. Neuroscience has faced criticism for a lack of reproducibility and reliable findings, often attributed to insufficient attention to statistical rigour in the face of complex datasets (Poldrack et al., 2017). Throughout the project, efforts were made to document and communicate the methods used to address the potential for false positives, particularly in analyses involving large numbers of statistical tests. This transparency is essential for fostering replicability and trust in the results. However, despite this transparency, follow-up studies are necessary to validate our cross-sectional findings.

8.7 Future Research

Building on the findings of this project, some interesting and promising avenues for future research to expand our understanding of the relationships between functional connectivity AD biomarkers ($A\beta$ and tau) could include the following:

1. A longitudinal component to measure functional connectivity with $A\beta$ -PET and tau-PET studies across multiple time points. This would allow for measuring potential changes and interactions over time. It also provides for the attainment of causal relationships.
2. Additionally, measuring individual functional connectivity patterns may help inform risk prediction models for those potentially at risk of developing AD in the future, as well as the development of simply measuring group-level differences (as was the case in this thesis). Studies such as Franzmeier et al. (2020), who emphasised a “patient-centred” approach, support this.
3. Another potential future research avenue stems from an unintended finding of Chapter 7, whereby some participants exhibited atypical patterns of tau spread, similar to Vogel et al. (2021). The relationships between functional connectivity and AD biomarkers (particularly tau) might interact with brain function differently between individuals. Further research into the relationships between these differences in spatial spread patterns may broaden our understanding of disease heterogeneity.
4. Lastly, this project focused on functional connectivity. It is likely that measuring connectivity in multiple ways, e.g., effective connectivity (the inference of directional effects between brain regions; Mohammadian et al., 2023) and structural connectivity (e.g., to visualise and measure white matter tracts; Bergamino et al., 2022) would enrich the findings of this project.

8.8 Conclusions

My research aimed to broaden our understanding of the relationships between resting-state functional connectivity and AD biomarkers - A β and tau. The methodological choices spanned both “data-driven” and “hypothesis-driven” approaches. I began at the highest spatial point of resolution - the whole brain - before homing in on smaller sets of brain areas (forming resting-state networks) implicated in the clinical progression of AD.

The key findings point towards group-level functional connectivity differences between AD stages. This allowed for the extraction of seed regions that explained the most variance at various stages along the AD continuum. Although differences at the earliest stages (CU and MCI) were only present when (a) these groups were further divided into sub-groups based on A β status and (b) differences were observed at the network level, we were able to extract the left thalamus, precuneus, and frontal gyri as ROIs for subsequent analyses.

Furthermore, regional tau moderated more relationships between functional connectivity and multidomain cognitive performance. However, this modifying effect was exclusively observed between various functional connections and visuospatial processing among CU participants. Among those with MCI, more relationships were significant, and more cognitive domains were affected by the modifying impact of AD biomarkers (particularly tau). The direction of these relationships also showed group-specific patterns between CU and MCI participants.

A final key finding was that lower functional connectivity within the MTL was associated with higher regional tau burden among CU participants, mainly those with higher cortical A β burden (A β +).

Together, these findings reinforce the potential of using functional connectivity measures in AD and dementia trials, particularly when methods utilising dimensionality reduction are employed to capture group-level differences in functional connectivity. Given the substantial impact of A β and tau burdens on these connectivity patterns, functional connectivity could serve as a valuable outcome measure for tracking disease progression or assessing therapeutic effects. However, whether functional connectivity can act as a robust and reliable *biomarker* remains uncertain.

Lastly, the human connectome - measured in this project at a macro-scale spatial resolution - represents a complex, high-dimensional dataset that requires substantial computational resources for meaningful interpretation. Analysing the thousands of functional connections across different stages of AD requires advanced computational techniques capable of distilling actionable insights. It is by leveraging these tools that we can deepen our understanding of the intricate relationships between functional connectivity patterns and AD biomarkers. By doing so, we can move towards gaining insight into the underlying neural mechanisms of AD and pave the way for more precise diagnostic and therapeutic strategies in the future.

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Appendices

Appendix 1.1 Inclusion Criteria for Disease Stage Cohorts in the ADNI-3 Study

	CN	Amnesic-MCI	Mild-AD
<i>Reported Memory complaints or concerns</i>	CN was defined as an older adult with or without subjective memory complaints. This was verified by a study partner.	Participant reported a subjective memory <i>concern</i> (by the participant, study partner, or a clinician).	Participant reported a subjective memory <i>concern</i>. Reported by participant, study partner, or clinician (as with MCI).
<i>Memory function (Wechsler)</i>	“Normal” memory function as determined by the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory scale. The minimum score for CN was weighted based on education level. More than or equal to nine for 16+ years of education, more than or equal to five for eight-15 years of education and more than or equal to three for zero-seven years of education.	“Abnormal” memory function as determined by Logical Memory II Subscale (Delayed Paragraph recall) from the Wechsler Memory scale. The minimum score for MCI was weighted based on education level. Less than 11 for 16+ years of education; less than or equal to 9 for eight-15 years of education; less than or equal to 6 for zero to seven years of education.	“Abnormal” memory function as determined by Logical Memory II Subscale (Delayed Paragraph recall) from the Wechsler Memory scale. The minimum score for AD was weighted based on education level. Less than or equal to 8 for 16+ years of education; less than or equal to four for eight-15 years of education; less than or equal to two for zero-seven years of education.

<i>Memory Function (MMSE)</i>	24-30 (exceptions made for participants with less than eight years of education).	Same as CN	20-26 (exceptions made for participants with less than eight years of education).
<i>CDR</i>	CDR = 0; Memory score = 0	CDR = 0.5; Memory score = 0.5	CDR = 0.5 or 1
<i>General cognitive function</i>	CN – based upon the absence of Significant cognitive impairment / day-to-day functionality.	Overall cognition and functionality preserved / AD diagnosis cannot be made.	The participant met the criteria for probable AD (NINCDS/ADRDA criteria were met).
<i>Medication</i>	Permitted medication taken for at least four weeks.	Same as CN plus Cholinesterase inhibitors and memantine were allowed if on stable use for 12 weeks prior to being screened.	Same as MCI
<i>Neurological disease (newly enrolled participants only)</i>	Any neurological disease, e.g., Parkinson's, Huntington's disease, etc. or known brain structural abnormalities, head trauma, etc.	Same as CN, except other than incipient AD	Same as CN and MCI, except other than AD

Notes: MMSE = Mini-mental state examination; CDR = Clinical Dementia Rating; CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease.

Appendix 1.2 Additional Inclusion and Exclusion Criteria – ADNI

<i>For newly enrolled participants (onto ADNI-3), additional exclusionary criteria included</i>	55-90 years of age.
	GDS <6.
	Study partner informant viable (10+ hours of contact per week).
	No significant visual and auditory impairments.
	No presence of disease that would be considered to interfere with the results collected in the study.
	Hachinski Ischemic Score (modified version) = less than or equal to four.
	Six grades (US) of education or sufficient evidence of “good working history”.
	Consented to longitudinal imaging scans.
	Consented to longitudinal samples.
	Fluency in English (or Spanish).
	Evidence of infection, infarction, or focal lesions or multiple lacunes during Baseline MRI.
	Contraindications evident for MRI.
	MDD, BD within the last year.
	History of schizophrenia.
	History of substance misuse (e.g., alcohol dependence) within the last two years.
	Illnesses deemed to potentially interfere with the participant complying with study protocols (e.g., chronic back pain for MRI scans).
	Clinically low B12 levels.
	Current use of psychoactive medications.

Notes: GDS = geriatric depression score; ADNI = Alzheimer's Disease Neuroimaging Initiative;
MDD = major depressive disorder; BD = bipolar disorder; OCD = obsessive compulsive disorder.

Appendix 1.3 Additional Exclusion Criteria – OASIS-3

Exclusion Criterion	Details
Medical conditions that precluded longitudinal participation	For example, end-stage renal disease
Medical contraindications	Having a pacemaker (specific exclusion criteria for MRI), anticoagulant use (specific exclusion criteria for lumbar puncture)
Cognitive status	Not meeting the required CDR score of ≤ 1 at the time of the most recent assessment.
General health screening for imaging contraindications	Contraindications to PET or MR imaging were assessed.
Specific health reasons that warranted exclusion	Women who were pregnant or breastfeeding
	Implanted medical devices (e.g., pacemakers)
	History or risk of metal in the eye
	History of Claustrophobia

Notes. MRI = magnetic resonance imaging; PET = positron emission tomography; CDR = Clinical Dementia Rating.

Appendix 4.1 Full Whole-Brain ROI-to-ROI With TFCE Results

Firstly, no significant differences in functional connectivity were found when comparing whole-brain functional connectivity between CU and MCI participants. Differences in functional connectivity were observed between CU and DAT and MCI and DAT.

Appendix 4.1.1 CU vs. Dementia due to AD

Twenty clusters survived TFCE correction (1000 permutations) when comparing whole-brain functional connectivity patterns between CU and DAT participants. Of the 95 total ROI-to-ROI surviving pairwise associations of the 20 clusters, 72 were significant to at least $p < .05$, four were trending significance at this level, and 19 were not statistically significant insignificant:

Cluster 1 of 20 (connections 1 to 7): All seven connections in this cluster were significant. (1) Frontoparietal network, left lateral prefrontal cortex – Salience network, left anterior insula, $T(247) = 5.75$, TFCE $p\text{-FDR} < .001$; (2) left middle frontal gyrus – Salience network, left anterior insula, $T(247) = 4.68$, TFCE $p\text{-FDR} = .003$; (3) Frontoparietal network, left lateral prefrontal cortex – left frontal operculum cortex, $T(247) = 3.75$, TFCE $p\text{-FDR} = .012$; (4) left middle frontal gyrus – left insular cortex, $T(247) = 3.56$, TFCE $p\text{-FDR} = .016$; (5) left middle frontal gyrus – left frontal operculum cortex, $T(247) = 3.51$, TFCE $p\text{-FDR} = .017$; (6) Frontoparietal network, right lateral prefrontal cortex – Salience network, left anterior insula, $T(247) = 3.34$, TFCE $p\text{-FDR} = .024$; (7) Frontoparietal network, right lateral prefrontal cortex – left insular cortex, $T(247) = 3.22$, TFCE $p\text{-FDR} = .031$.

Cluster 2 of 20 (connections 8 to 9): Both connections were significant. (8) left thalamus – left amygdala, $T(247) = 5.49$, TFCE $p\text{-FDR} = .001$; (9) right thalamus – left amygdala, $T(247) = 4.03$, TFCE $p\text{-FDR} = .007$.

Cluster 3 of 20 (connections 10 to 12): All three connections were significant. (10) Cingulate gyrus, posterior division – left temporal pole, $T(247) = 5.27$, TFCE $p\text{-FDR} = .001$; (11) Cingulate gyrus,

posterior division – left parahippocampal gyrus, anterior division, $T(247) = 4.03$, $p\text{-FDR} = .007$; (12) left thalamus - left parahippocampal gyrus, anterior division, $T(247) = 3.32$, $p\text{-FDR} = .026$.

Cluster 4 of 20 (connections 13 to 14): Both connections were significant. (13) right juxtapositional lobule cortex (formerly supplementary motor cortex) – Visual network, medial portion, $T(247) = -4.80$, $\text{TFCE } p\text{-FDR} = .002$; (14) left juxtapositional lobule cortex (formerly supplementary motor cortex) – Visual network, left lateral portion, $T(247) = -4.04$, $\text{TFCE } p\text{-FDR} = .007$.

Cluster 5 of 20 (connections 15 to 16): One connection was significant, and one was trending. (15) right pallidum – right temporal fusiform cortex, posterior division, $T(247) = 5.11$, $\text{TFCE } p\text{-FDR} = .002$; (16) right pallidum – right parahippocampal gyrus, anterior division, $T(247) = 2.92$, $\text{TFCE } p\text{-FDR} = .051$.

Cluster 6 of 20 (connections 17 to 22): All six connections were significant. (17) Right inferior frontal gyrus (pars triangularis) – left putamen, $T(247) = -4.61$, $\text{TFCE } p\text{-FDR} = .003$; (18) right inferior frontal gyrus (pars opercularis) – left pallidum, $T(247) = -4.49$, $\text{TFCE } p\text{-FDR} = .003$; (19) Language network, right inferior frontal gyrus – left putamen, $T(247) = -4.21$, $\text{TFCE } p\text{-FDR} = .005$; (20) right frontal pole – left putamen, $T(247) = -3.85$, $\text{TFCE } p\text{-FDR} = .010$; (21) Language network, right inferior frontal gyrus – left pallidum, $T(247) = -3.62$, $\text{TFCE } p\text{-FDR} = .015$; (22) right inferior frontal gyrus (pars triangularis) – left pallidum, $T(247) = -3.30$, $\text{TFCE } p\text{-FDR} = .025$.

Cluster 7 of 20 (connections 23 to 25): All three connections were significant. (23) Right thalamus – right cerebellum (crus2), $T(247) = 4.61$, $\text{TFCE } p\text{-FDR} = .003$; (24) left thalamus – right cerebellum (crus2), $T(247) = 3.94$, $\text{TFCE } p\text{-FDR} = .009$; (25) right thalamus – right cerebellum (crus1), $T(247) = 3.58$, $\text{TFCE } p\text{-FDR} = .015$.

Cluster 8 of 20 (connections 26 to 30): All five connections were significant. (26) Right inferior frontal gyrus (pars triangularis) – right cerebellum (6), $T(247) = 4.73$, $\text{TFCE } p\text{-FDR} = .003$; (27) Language

network, right inferior frontal gyrus – right cerebellum (6), $T(247) = 4.10$, TFCE p -FDR = .007; (28) Language network, right inferior frontal gyrus – left cerebellum (6), $T(247) = 3.60$, TFCE p -FDR = .015; (29) right inferior frontal gyrus (pars triangularis) – left cerebellum (6), $T(247) = 3.47$, TFCE p -FDR = .019; (30) Language network, right inferior frontal gyrus - vermis 8, $T(247) = 3.24$, TFCE p -FDR = .030.

Cluster 9 of 20 (connections 31 to 38): Of the eight connections, five were significant, one trending, and two were not statistically significant. (31) Right inferior frontal gyrus (pars opercularis) – right angular gyrus, $T(247) = 5.03$, TFCE p -FDR = .002; (32) right inferior frontal gyrus (pars opercularis) – Frontoparietal network, right posterior parietal cortex, $T(247) = 4.25$, TFCE p -FDR = .005; (33) right inferior frontal gyrus (pars triangularis) – right angular gyrus, $T(247) = 3.60$, TFCE p -FDR = .015; (34) right inferior frontal gyrus (pars opercularis) – Default Mode network, right lateral parietal cortex, $T(247) = 3.20$, TFCE p -FDR = .032; (35) Language network, right inferior frontal gyrus – Frontoparietal network, right posterior parietal cortex, $T(247) = 2.97$, TFCE p -FDR = .047; (36) right inferior frontal gyrus (pars triangularis) – Frontoparietal network, right posterior parietal cortex, $T(247) = 2.91$, TFCE p -FDR = .052; (37) right inferior frontal gyrus (pars triangularis) – Default Mode network, right lateral parietal cortex, $T(247) = 2.78$, TFCE p -FDR = .064; (38) LAN, right IFG – right angular gyrus, $T(247) = 2.76$, TFCE p -FDR = .067.

Cluster 10 of 20 (connection 39): One of the one connection was significant. (39) right middle temporal gyrus (temporooccipital part) – vermis (8), $T(247) = 4.40$, TFCE p -FDR = .004.

Cluster 11 of 20 (connections 40 to 45): All six connections were significant. (40) left planum polare – precuneus, $T(247) = 4.54$, TFCE p -FDR = .003; (41) left planum polare – Default Mode network, posterior cingulate cortex, $T(247) = 3.61$, TFCE p -FDR = .015; (42) left insular cortex – Default Mode network, posterior cingulate cortex, $T(247) = 3.55$, TFCE p -FDR = .016; (43) Salience network, left anterior insula - precuneus, $T(247) = 3.46$, TFCE p -FDR = .019; (44) left insular cortex – precuneus,

T(247) = 3.19, TFCE p -FDR = .033; (45) Salience network, left anterior insula – Default Mode network, posterior cingulate cortex, T(247) = 3.05, TFCE p -FDR = .040.

Cluster 12 of 20 (connections 46 to 47): Both connections were significant. (46) right middle temporal gyrus (temporooccipital part) – right cerebellum (6), T(247) = 4.31, TFCE p -FDR = .004; (47) right middle temporal gyrus (temporooccipital part) – Cerebellar network, anterior portion, T(247) = 3.95, TFCE p -FDR = .009.

Cluster 13 of 20 (connections 48 to 56): Five of the nine connections were significant, one was trending, and three were not statistically significant. (48) Language network, right inferior frontal gyrus – right lateral occipital cortex, inferior division, T(247) = 4.91, TFCE p -FDR = .002; (49) right inferior frontal gyrus (pars triangularis) – right lateral occipital cortex, inferior division, T(247) = 4.35, TFCE p -FDR = .004; (50) right inferior frontal gyrus (pars triangularis) – Visual network, right lateral portion, T(247) = 3.31, TFCE p -FDR = .026; (51) right inferior frontal gyrus (pars triangularis) – right occipital fusiform gyrus, T(247) = 3.25, TFCE p -FDR = .029; (52) Language network, right inferior frontal gyrus – Visual network, right lateral portion, T(247) = 2.98, TFCE p -FDR = .046; (53) right inferior frontal gyrus (pars triangularis) – left occipital fusiform gyrus, T(247) = 2.89, TFCE p -FDR = .054; (54) Language network, right inferior frontal gyrus – left occipital fusiform gyrus, T(247) = 2.68, TFCE p -FDR = .075; (55) Language network, right inferior frontal gyrus – left inferior lateral occipital cortex, T(247) = 2.48, TFCE p -FDR = .102; (56) Language network, right inferior frontal gyrus – right occipital fusiform gyrus, T(247) = 2.04, TFCE p -FDR = .191.

Cluster 14 of 20 (connections 57 to 58): Both connections were significant. (57) Dorsal Attention network, left intraparietal sulcus – left paracingulate gyrus, T(247) = 4.92, TFCE p -FDR = .002; (58) left superior parietal lobule – left paracingulate gyrus, T(247) = 4.66, TFCE p -FDR = .003.

Cluster 15 of 20 (connection 59): One of the connections was significant. (59) cingulate gyrus, posterior division – Visual network, occipital portion, T(247) = 4.82, TFCE p -FDR = .002.

Cluster 16 of 20 (connections 60 to 65): Of the six connections, four were significant, one was trending, and one was not statistically significant. (60) right inferior frontal gyrus (pars triangularis) – right temporal fusiform cortex, anterior division, $T(247) = 4.70$, TFCE p -FDR = .003; (61) Language network, right inferior frontal gyrus – right inferior temporal gyrus, anterior division, $T(247) = 4.13$, TFCE p -FDR = .006; (62) Language network, right inferior frontal gyrus – right temporal fusiform cortex, anterior division, $T(247) = 3.87$, TFCE p -FDR = .001; (63) Language network, right inferior frontal gyrus – right middle temporal gyrus, anterior division, $T(247) = 2.97$, TFCE p -FDR = .047; (64) right inferior frontal gyrus (pars triangularis) – right inferior temporal gyrus, anterior division, $T(247) = 2.93$, TFCE p -FDR = .051; (65) right inferior frontal gyrus (pars opercularis) – right anterior middle temporal gyrus, $T(247) = 2.45$, TFCE p -FDR = .107.

Cluster 17 of 20 (connections 66 to 70): Of the five connections, four were significant, and one was not statistically significant. (66) left putamen – right temporal fusiform cortex, anterior division, $T(247) = 4.15$, TFCE p -FDR = .006; (67) left putamen – right inferior temporal gyrus, anterior division, $T(247) = 3.80$, TFCE p -FDR = .011; (68) left pallidum – right middle temporal gyrus, anterior division, $T(247) = 3.69$, TFCE p -FDR = .013; (69) right pallidum – right inferior temporal gyrus, anterior division, $T(247) = 3.00$, TFCE p -FDR = .045; (70) left pallidum – right anterior ITG, $T(247) = 2.67$, TFCE p -FDR = .076.

Cluster 18 of 20 (connections 71 to 82): Of the 12 connections, only five were significant, and seven were not statistically significant. (71) cingulate gyrus, anterior division – left temporal fusiform cortex, anterior division, $T(247) = -4.97$, TFCE p -FDR = .002; (72) right paracingulate gyrus – left temporal fusiform cortex, anterior division, $T(247) = -3.75$, TFCE p -FDR = .012; (73) right paracingulate gyrus – left parahippocampal gyrus, anterior division, $T(247) = -3.66$, TFCE p -FDR = .014; (74) left paracingulate gyrus – left parahippocampal gyrus, anterior division, $T(247) = -3.24$, TFCE p -FDR = .030; (75) right paracingulate gyrus – left temporal pole, $T(247) = -3.07$, TFCE p -FDR = .040; (76) anterior cingulate gyrus – left temporal pole, $T(247) = -2.49$, TFCE p -FDR = .102; (77) left

paracingulate gyrus – left temporal pole, $T(247) = -2.31$, TFCE p -FDR = .133; (78) left paracingulate gyrus – left anterior temporal fusiform cortex, $T(247) = -2.23$, TFCE p -FDR = .148; (79) SAL, anterior cingulate cortex – left temporal pole, $T(247) = -1.99$, TFCE p -FDR = .204; (80) SAL, anterior cingulate cortex – left anterior temporal fusiform cortex, $T(247) = -1.89$, TFCE p -FDR = .230; (81) right paracingulate gyrus – left amygdala, $T(247) = -1.72$, TFCE p -FDR = .283; (82) anterior cingulate cortex – right temporal pole, $T(247) = -1.67$, TFCE p -FDR = .300.

Cluster 19 of 20 (connections 83 to 91): Of the nine connections, only four were significant, and five were not statistically significant. (83) left supramarginal gyrus, anterior division – right cerebellum (10), $T(247) = 4.68$, TFCE p -FDR = .003; (84) Sensorimotor network, left lateral portion – right cerebellum (10), $T(247) = 4.48$, TFCE p -FDR = .003; (85) left supramarginal gyrus, anterior division - brain-stem, $T(247) = 3.76$, TFCE p -FDR = .012; (86) left supramarginal gyrus, anterior division – right cerebellum (3), $T(247) = 3.76$, TFCE p -FDR = .012; (87) Sensorimotor network, left lateral portion – right cerebellum (3), $T(247) = 2.52$, TFCE p -FDR = .100; (88) left anterior supramarginal gyrus – left cerebellum (3), $T(247) = 2.36$, TFCE p -FDR = .124; (89) Left SAL, supramarginal gyrus - brain-stem, $T(247) = 2.36$, TFCE p -FDR = .124; (90) SMN, left lateral portion - brain-stem, $T(247) = 2.13$, TFCE p -FDR = .170; (91) SAL, left supramarginal gyrus – right cerebellum (3), $T(247) = 1.91$, TFCE p -FDR = .227.

Cluster 20 of 20 (connections 92 to 95): All four connections were significant. (92) Visual network, occipital portion – Default Mode network, left lateral parietal cortex, $T(247) = 4.63$, TFCE p -FDR = .003; (93) Visual network, occipital portion – Default Mode network, posterior cingulate cortex, $T(247) = 4.24$, TFCE p -FDR = .005; (94) Visual network, occipital portion – left lateral occipital cortex, superior division, $T(247) = 3.89$, TFCE p -FDR = .001; (95) Visual network, occipital portion – precuneus, $T(247) = 3.85$, TFCE p -FDR = .010.

Frequency Chart Showing the Number of Times Each Brain Region Showed Significant and Trending Level Differences in Functional Connectivity (CU vs. Dementia Due to AD).

ROI	Cluster #.																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total
Right inferior frontal gyrus (pars triangularis)						2		2	2				4			2					12
Language network, right inferior frontal gyrus						2		3	1				2			3					11
Left putamen						3											2				5
Salience network, left anterior insula	3										2										5
Visual network (occipital portion)															1					4	5
Default Mode network, posterior cingulate cortex											3									1	4
Left insular cortex	2										2										4
Left pallidum						3											1				4
Left parahippocampal gyrus (anterior division)			2															2			4

Precuneus										3									1	4
Right inferior frontal gyrus (pars opercularis)					1			3												4
Right inferior temporal gyrus (anterior division)															2	2				4
Cingulate gyrus (posterior division)			2											1						3
Frontoparietal network, right posterior parietal cortex								3												3
Left middle frontal gyrus	3																			3
Left paracingulate gyrus													2				1			3
Left supramarginal gyrus (anterior portion)																		3		3
Left thalamus		1	1				1													3
Right cerebellum (lobule 6)								2			1									3
Right middle temporal gyrus (temporooccipital part)									1		2									3

Right pallidum					2												1				3
Right paracingulate gyrus																		3			3
Right temporal fusiform cortex (anterior division)															2		1				3
Right thalamus		1					2														3
Default Mode network, right lateral parietal cortex								2													2
Frontoparietal network, left lateral prefrontal cortex	2																				2
Frontoparietal network, right lateral prefrontal cortex	2																				2
Left amygdala		2																			2
Left cerebellum (lobule 6)								2													2
Left frontal operculum	2																				2
Left planum polare											2										2

Left temporal fusiform cortex (anterior division)																	2			2
Left temporal pole			1														1			2
Right angular gyrus								2												2
Right cerebellum (crus2)							2													2
Right cerebellum (lobule 10)																		2		2
Right lateral occipital cortex (inferior portion)												2								2
Right middle temporal gyrus (anterior division)															1	1				2
Vermis (lobule 8)								1		1										2
Visual network (right lateral portion)												2								2
Right Cerebellum (lobule 3)																		1		1
Sensorimotor network (left lateral portion)																		1		1

Brainstem																		1		1
Cerebellar network (anterior portion)											1									1
Cingulate gyrus (anterior division)																		1		1
Default Mode network, left lateral parietal cortex																			1	1
Dorsal Attention network, left intraparietal sulcus													1							1
Left juxtapositional lobule				1																1
Left lateral occipital cortex (superior division)																			1	1
Left occipital fusiform gyrus												1								1
Left superior parietal lobule													1							1
Right cerebellum (crus1)							1													1
Right frontal pole						1														1

Right juxtapositional lobule				1																1
Right occipital fusiform gyrus												1								1
Right parahippocampal gyrus (anterior division)					1															1
Right temporal fusiform cortex (posterior division)					1															1
Visual network (left lateral portion)				1																1
Visual network (medial portion)				1																1

Notes. CU = cognitively unimpaired; DAT = dementia due to Alzheimer's disease.

Appendix 4.1.2 MCI vs. Dementia Due to AD

Cluster 1 of 12 (connections 1 to 12): Of the 12 connections, eight were significant, one was trending significance, and three were non-significant: (1) left superior parietal lobule – right inferior temporal gyrus (temporooccipital part), $T(247) = -4.99$, TFCE p -FDR = .003; (2) Dorsal Attention network, left intraparietal sulcus – right inferior temporal gyrus (temporooccipital part), $T(247) = -4.23$, TFCE p -FDR = .007; (3) right superior parietal lobule – right inferior temporal gyrus (temporooccipital part), $T(247) = -3.97$, TFCE p -FDR = .010; (4) Dorsal Attention network, right intraparietal sulcus – right inferior temporal gyrus (temporooccipital part), $T(247) = -3.73$, TFCE p -FDR = .015; (5) right postcentral gyrus – right inferior temporal gyrus, posterior division, $T(247) = -3.55$, TFCE p -FDR = .022; (6) right precentral gyrus – right inferior temporal gyrus, temporooccipital part, $T(247) = -3.48$, TFCE p -FDR = .024; (7) right superior parietal lobule – right inferior temporal gyrus, posterior division, $T(247) = -3.21$, TFCE p -FDR = .038; (8) Dorsal Attention network, left intraparietal sulcus – right inferior temporal gyrus, posterior division, $T(247) = -2.60$, TFCE p -FDR = .042; (9) Dorsal Attention network, right intraparietal sulcus – right inferior temporal gyrus, posterior division, $T(247) = -3.02$, TFCE p -FDR = .054; (10) left superior parietal lobule – right posterior inferior temporal gyrus, $T(247) = -2.57$, TFCE p -FDR = .100; (11) right postcentral gyrus - right inferior temporal gyrus (temporooccipital part), $T(247) = -2.54$, p -FDR = .103; (12) right postcentral gyrus – right temporal occipital fusiform cortex, $T(247) = -2.30$, TFCE p -FDR = .146.

Cluster 2 of 12 (connections 13 to 25): Five connections were significant, and eight were insignificant: (13) cingulate gyrus, anterior division – left temporal fusiform cortex, anterior division, $T(247) = -5.20$, TFCE p -FDR = .002; (14) right paracingulate gyrus – left parahippocampal gyrus, anterior division, $T(247) = -4.42$, TFCE p -FDR = .005; (15) right paracingulate gyrus – left temporal fusiform cortex, anterior division, $T(247) = -3.83$, TFCE p -FDR = .013; (16) right paracingulate gyrus – left temporal pole, $T(247) = -3.46$, TFCE p -FDR = .025; (17) left paracingulate gyrus – left parahippocampal gyrus, anterior division, $T(247) = -3.32$, TFCE p -FDR = .031; (18) Salience network, anterior cingulate cortex – left anterior temporal fusiform cortex, $T(247) = -2.93$, TFCE p -FDR = .061; (19) anterior cingulate

gyrus – left temporal pole, $T(247) = -2.92$, TFCE p -FDR = .062; (20) left paracingulate gyrus – left anterior temporal fusiform cortex, $T(247) = -2.76$, TFCE p -FDR = .077; (21) left paracingulate gyrus – left temporal pole, $T(247) = -2.51$, TFCE p -FDR = .110; (22) Salience network, anterior cingulate cortex – left temporal pole, $T(247) = -2.00$, TFCE p -FDR = .214; (23) right paracingulate gyrus – left amygdala, $T(247) = -1.73$, TFCE p -FDR = .300; (24) anterior cingulate gyrus – right temporal pole, $T(247) = -1.69$, TFCE p -FDR = .307; (25) right superior frontal gyrus – left parahippocampal cortex (anterior portion), $T(247) = -1.69$, TFCE p -FDR = .310.

Cluster 3 of 12 (connections 26 to 29): Three of the four connections were significant, and one was not statistically significant: (26) Sensorimotor network, superior division – right inferior temporal gyrus (temporooccipital part), $T(247) = -5.18$, p -FDR = .002; (27) left precentral gyrus – right inferior temporal gyrus (temporooccipital part), $T(247) = -4.32$, p -FDR = .006; (28) Sensorimotor network, superior portion – right inferior temporal gyrus, posterior division, $T(247) = -3.82$, p -FDR = .013; (29) right Juxtapositional lobule cortex (formerly supplementary motor cortex) – right inferior temporal gyrus (temporooccipital part), $T(247) = -2.69$, p -FDR = .085.

Cluster 4 of 12 (connections 30 to 32): All three connections were significant: (30) left planum temporale – Frontoparietal network, left posterior parietal cortex, $T(247) = 4.68$, p -FDR = .005; (31) left superior temporal gyrus, posterior division – Frontoparietal network, left posterior parietal cortex, $T(247) = 4.68$, p -FDR = .005; (32) left superior temporal gyrus, posterior division – left angular gyrus, $T(247) = 3.31$, p -FDR = .032.

Cluster 5 of 12 (connections 33 to 34): Both connections were significant: (33) Dorsal Attention network, left intraparietal sulcus – left paracingulate gyrus, $T(247) = 4.64$, TFCE p -FDR = .005; (34) left superior parietal lobule – left paracingulate gyrus, $T(247) = 4.51$, TFCE p -FDR = .005.

Cluster 6 of 12 (connections 35 to 36): Both connections were significant: (35) left planum polare – precuneus, $T(247) = 4.41$, TFCE p -FDR = .005; (36) left planum polare – Default Mode network, posterior cingulate cortex, $T(247) = 3.74$, TFCE p -FDR = .015.

Cluster 7 of 12 (connections 37 to 39): All three connections were significant: (37) Salience network, left anterior insula – left lateral occipital cortex, superior division, $T(247) = 4.24$, TFCE p -FDR = .007; (38) left insular cortex – left lateral occipital cortex, superior division, $T(247) = 3.99$, TFCE p -FDR = .010; (39) left planum polare – right lateral occipital cortex, superior division, $T(247) = 3.57$, TFCE p -FDR = .021.

Cluster 8 of 12 (connections 40 to 48): Of the nine connections, six were significant, and three were trending significance: (40) right caudate – right cerebellum (6), $T(247) = 4.03$, TFCE p -FDR = .009; (41) left caudate – left cerebellum (6), $T(247) = 3.77$, TFCE p -FDR = .014; (42) right caudate – vermis (8), $T(247) = 3.70$, TFCE p -FDR = .017; (43) right caudate – left cerebellum (6), $T(247) = 3.55$, TFCE p -FDR = .022; (44) left putamen – left cerebellum (6), $T(247) = 3.44$, TFCE p -FDR = .025; (45) left caudate – Cerebellar network, anterior portion, $T(247) = 3.39$, TFCE p -FDR = .027; (46) right caudate – vermis (7), $T(247) = 3.07$, TFCE p -FDR = .050; (47) left putamen – right cerebellum (6), $T(247) = 3.05$, TFCE p -FDR = .051; (48) left caudate – vermis (7), $T(247) = 2.99$, TFCE p -FDR = .056.

Cluster 9 of 12 (connections 49 to 51): All three connections were significant. (49) right pallidum – right lateral occipital cortex, inferior division, $T(247) = 4.46$, TFCE p -FDR = .005; (50) right pallidum – right occipital fusiform gyrus, $T(247) = 3.94$, TFCE p -FDR = .011; (51) left pallidum – right lateral occipital cortex, inferior division, $T(247) = 3.52$, TFCE p -FDR = .022.

Cluster 10 of 12 (connections 52 to 58) Comprised seven connections, four of which were statistically significant, and three were not statistically significant. (52) Frontoparietal network, left lateral prefrontal cortex – Salience network, left anterior insula, $T(247) = 4.79$, TFCE p -FDR = .004; (53) left middle frontal gyrus – Salience network, left anterior insula, $T(247) = 4.24$, TFCE p -FDR = .007; (54)

left middle frontal gyrus – left insular cortex, $T(247) = 3.28$, TFCE p -FDR = .034; (55) Frontoparietal network, left lateral prefrontal cortex – left frontal operculum cortex, $T(247) = 3.11$, TFCE p -FDR = .046. (56) Salience network, left rostral prefrontal cortex – left insular cortex, $T(247) = 2.93$, TFCE p -FDR = .061; (57) left middle frontal gyrus – left frontal operculum, $T(247) = 2.88$, TFCE p -FDR = .065; (58) Salience network, left rostral prefrontal cortex – Salience network, left anterior insula. $T(247) = 2.72$, TFCE p -FDR = .081.

Cluster 11 of 12 (connections 59 to 65): Of the seven connections, two were significant, one was trending significance, and four were not statistically significant: (59) left central opercular cortex – right hippocampus, $T(247) = -5.27$, TFCE p -FDR = .002; (60) left central opercular cortex – right parahippocampal cortex, posterior division, $T(247) = -3.59$, TFCE p -FDR = .020; (61) left central opercular cortex – right amygdala, $T(247) = -3.07$, TFCE p -FDR = .050. (62) left Heschl's gyrus – right hippocampus, $T(247) = -2.48$, TFCE p -FDR = .113; (63) left Heschl's gyrus – right parahippocampal gyrus (posterior division), $T(247) = -2.40$, TFCE p -FDR = .130; (64) left planum temporale – right hippocampus, $T(247) = -2.28$, TFCE p -FDR = .150; (65) left Heschl's gyrus – vermis (lobule 12), $T(247) = -2.25$, TFCE p -FDR = .156.

Cluster 12 of 12 (connections 66 to 68): All three connections were significant: (66) left Heschl's gyrus – Salience network, left supramarginal gyrus, $T(247) = 4.54$, TFCE p -FDR = .005; (67) left central opercular cortex – left supramarginal gyrus, posterior division, $T(247) = 3.88$, TFCE p -FDR = .012; (68) left central opercular cortex – Salience network, left supramarginal gyrus, $T(247) = 3.23$, TFCE p -FDR = .037.

Frequency Chart Showing the Number of Times Each Brain Region Showed Trending Level Differences in Functional Connectivity (MCI vs. Dementia Due to AD).

ROI	Cluster #.												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Right inferior temporal gyrus (temporooccipital part)	5		2										7
Right inferior temporal gyrus (posterior division)	4		1										5
Left central opercular cortex											3	2	5
Right caudate								4					4
Left planum temporale				1		2							3
Dorsal Attention network (left intraparietal sulcus)	2				1								3
Left caudate								3					3

Left cerebellum (lobule 6)							3					3
Left paracingulate gyrus		1		2								3
Right paracingulate gyrus		3										3
Salience network, left anterior insula						1			2			3
Dorsal Attention network (right intraparietal sulcus)	2											2
Frontoparietal network, left lateral prefrontal cortex									2			2
Frontoparietal network, left posterior parietal cortex			2									2
Left insular cortex						1			1			2
Left lateral occipital cortex (superior division)						2						2
Left middle frontal gyrus									2			2

Left parahippocampal gyrus (anterior division)		2										2
Left putamen							2					2
Left superior parietal lobule	1				1							2
Left superior temporal gyrus (posterior division)				2								2
Left temporal fusiform cortex (anterior division)		2										2
Right cerebellum (lobule 6)							2					2
Right lateral occipital cortex (inferior division)								2				2
Right pallidum								2				2
Right superior parietal lobule	2											2
Salience network, left supramarginal gyrus											2	2
Sensorimotor network (superior portion)			2									2

Vermis (lobule 7)								2					2
Cerebellar network (anterior)								1					1
Cingulate gyrus (anterior division)		1											1
Default Mode network, posterior cingulate cortex						1							1
Left angular gyrus				1									1
Left frontal operculum										1			1
Left Heschl's gyrus												1	1
Left pallidum									1				1
Left planum polare								1					1
Left precentral gyrus			1										1
Left supramarginal gyrus (posterior division)												1	1
Left temporal pole		1											1

Precuneus						1							1
Right amygdala											1		1
Right hippocampus											1		1
Right lateral occipital cortex (superior division)							1						1
Right occipital fusiform gyrus									1				1
Right parahippocampal gyrus (posterior division)											1		1
Right postcentral gyrus	1												1
Right precentral gyrus	1												1
Vermis (lobule 8)								1					1

Notes. MCI = mild cognitive impairment; DAT = dementia due to Alzheimer's disease.