BRAIN STRUCTURE AND CONNECTIVITY AS PREDICTORS OF FUNCTIONAL DECLINE AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

Dr Malgorzata Raczek

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ABSTRACT

Background

Neuropsychiatric symptoms affect most people with Alzheimer's disease (AD) and have previously been associated with structural and functional brain changes. Decline in the ability to perform activities of daily living (ADL) is a core feature of AD. This study aimed to establish whether there were structural and functional neural correlates at baseline that predicted faster decline in ADL as well as the emergence and severity of neuropsychiatric symptoms at 3 year follow-up.

Method

One hundred and eighty (n=180) patients with a diagnosis of AD, amnestic mild cognitive impairment (aMCI), or subjective cognitive decline (SCD) had a magnetic resonance imaging (MRI) scan at their initial assessment in memory clinic. Of those, 148 patients met the inclusion/exclusion criteria for this study and were invited to participate. Seventy nine of those (44 male, 35 female), consented to participate and were followed up at 3 years. The follow-up assessment of cognitive and functional status repeated clinical measures used at baseline, including Adenbrooke's Cognitive Examination - Revised (ACE-R) and Bristol Activities of Daily Living Scale (BADLS). Data relating to neuropsychiatric symptoms were measured with Neuropsychiatric Inventory (NPI). Additionally, the clinical assessment collected information relating to educational status, place of residence and co-morbidities.

T1 and T2* MRI were obtained at baseline using the Siemens Avanto 1.5 T scanner for volumetric and resting-state functional MRI (rs-fMRI) analysis. Pre-processing of the images was performed with statistical parametric mapping 12th edition (SPM12) voxel-based morphometry (VBM) pipeline for the structural imaging and FMRIB software library (FSL) package for the rs-fMRI. The correlation analysis was performed between the change in ADL status as measured by BADLS and neuropsychiatric symptoms as measured by NPI and the regional brain volume and activity in resting state networks.

Results

At baseline, 29 participants met the diagnostic criteria for AD, whereas 50 had a non-AD diagnosis of either aMCI (n=42) or SCD (n=8). At 3-year follow-up, 53 participants met the criteria for AD and 26 had a non-AD diagnosis.

VBM analysis showed negative correlation with regional grey matter (GM) volume at baseline and presence of neuropsychiatric symptoms at 3-year follow up in people with AD. Brain regions that correlated negatively with anxiety included anterior/middle cingulate cortex, which has previously been implicated in affective processing and links to default mode network (DMN). Orbitofrontal cortex and cerebellum volumes correlated negatively with high scores in total NPI score and in Psychosis sub-syndrome.

Brain connectivity analysis in participants with AD at follow-up (n=41) showed positive correlation between neuropsychiatric symptoms and connectivity in DMN as well as in the salience, as well as left and right frontoparietal networks. There was a negative correlation between connectivity in DMN and appetite.

We did not find significant correlation between ADL and regional GM volume or brain connectivity.

Conclusions

Neuropsychiatric symptoms in AD may be associated with regional atrophy and altered connectivity in brain networks that precede the onset of symptoms. Whilst this may signal a potential of using structural and functional brain imaging in improving prognosis for people with AD, the associations are complex and may follow a non-linear trajectory of change, especially in functional connectivity changes. Studies on larger population and with a wider range of functional ability and neuropsychiatric symptoms may further improve our knowledge about the potential of imaging data in predicting the course of illness for individual patients.

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ACRONYMS AND DEFINITIONS

aADL	advanced Activities of Daily Living
Aβ	Amyloid β
ACC	Anterior Cingulate Cortex
ACE	Addenbrooke's Cognitive Examination
ACE-R	Addenbrooke's Cognitive Examination - Revised
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AF	Atrial Fibrillation
ALFF	Amplitude of Low Frequency Fluctuations
AMB	Aberrant Motor Behaviour
aMCI	amnestic Mild Cognitive Impairment
APP	Amyloid Precursor Protein
ASL	Arterial Spin Labelling
BA	Brodmann Area
BADLS	Bristol Activities of Daily Living Scale

BOLD	Blood Oxygenation Level Dependent
BPSD	Behavioural and Psychological Symptoms of Dementia
CAA	Cerebral Amyloid Angiopathy
CAT12	Computational Anatomy Toolbox for SPM12
CBF	Cerebral Blood Flow
CERAD	Consortium to Establish a Registry for AD
CISC	Clinical Imaging Sciences Centre
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DIAN	Dominantly Inherited Alzheimer's disease Network
DLB	Dementia with Lewy Bodies
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DMT2	Diabetes Mellitus Type 2
DTI	Diffusion Tensor Imaging
EPI	Echo-Planar-Imaging
ETL	Echo Train Length

EYO	Estimated Years to Onset
FA	Fractional Anisotrophy
FDA	Food and Drug Administration
FDG	Fluorodextroglucose
FEAT	FMRI Expert Analysis Tool
FLAIR	Fast Fluid Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FOV	Field-Of-View
FPN	Frontoparietal Network
FSL	FMRIB Software Library
FTD	Frontotemporal Dementia
FTDbv	behavioural variant of Frontotemporal Dementia
FTLD	Frontotemporal Lobar Degeneration
FWE	Family-Wise Error
GCA	Global Cortical Atrophy
GDS	Geriatric Depression Scale
GICA	Group Independent Component Analysis

GLM	General Linear Model
GM	Grey Matter
GUI	Graphical User Interface
Hb	Haemoglobin
HDRS	Hamilton Depression Rating Scale
HRF	Haemodynamic Response Function
HT	Hypertension
IADL	Instrumental Activities of Daily Living
ICA	Independent Component Analysis
ICT	Information and Communication Technologies
IFG	Inferior Frontal Gyrus
IHD	Ischaemic Heart Disease
ITG	Inferior Temporal Gyrus
LC	Locus Coeruleus
LFP	Left Frontoparietal
MAS	Memory Assessment Service
MBI	Mild Behavioural Impairment

MBI-C	Mild Behavioral Impairment - Checklist
MCI	Mild Cognitive Impairment
MCFLIRT	Intra-Modal Fully Automated Motion Correction Tool
MEM	Memory
MELODIC	Multivariate Exploratory Linear Optimised Decomposition into Independent Components
MFG	Middle Frontal Gyrus
MTA	Medial Temporal lobe Atrophy
MTG	Middle Temporal Gyrus
ML	Machine Learning
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MPRAGE	Magnetisation Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging - Alzheimer's Association
NINDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke - Alzheimer's Disease and Related Disorders Association
NMDA	N-Methyl-D-Aspartate

NM-MRI	Neuromelanin-sensitive MRI
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric Symptoms
NFT	Neurofibrillary Tangles
Lang.	Language
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PiB PET	Pittsburgh compound B PET
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PAQUID	Personnees Agees QUID
PSEN1	Presenilin 1
PSEN2	Presenilin 2
OFC	Orbitofrontal Cortex
OR	Odds Ratio
rAI	right Anterior Insula
rDLPFC	right Dorsolateral Prefrontal Cortex

rCBF	regional Cerebral Blood Flow
RCT	Randomised Controlled Trial
RF	Radiofrequency
RFP	Right Frontoparietal
ROI	Region Of Interest
rPCC	right Posterior Cingulate Cortex
rs-fMRI	resting state functional Magnetic Resonance Imaging
SAL	Salience Network
SBM	Surface Based Morphometry
SCD	Subjective Cognitive Decline
SD	Standard Deviation
SFG	Superior Frontal Gyrus
SMG	Supramarginal Gyrus
SPECT	Single Proton Emission Computed Tomography
SPM12	Statistical Parametric Mapping 12 edition
SPSS	Statistical Package for Social Sciences
STG	Superior Temporal Gyrus

SVD	Small Vessel Disease
SVM	Support Vector Machine
TDP-43	Transactive Response Deoxyribonucleic Acid Binding Protein 43
TE	Echo Time
TFCE	Threshold-Free Cluster Enhancement
TR	Repetition Time
TSE	Turbo Spin Echo
TUG	Timed Up and Go
UPDRS	Unified Parkinson's Disease Rating Scale
VBM	Voxel-Based Morphometry
VMPFC	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area
WM	White Matter
WML	White Matter Lesions

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I dedicate this thesis to Wojtek Bilski

DECLARATION

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed:

Dated: 24 December 2022

CHAPTER 1. INTRODUCTION AND BACKGROUND

Dementia is a common and serious condition in later life, affecting about 47 million people worldwide (Prince et al., 2016). At its core is a progressive decline in cognition and ability to complete activities of daily living (ADL) (Ballard et al., 2011). People with dementia show variability in the rate of functional decline, whilst the associations between cognitive and functional impairment are not straightforward, especially in mild disease severity (Liu-Seifert et al., 2015). Most people with dementia will develop distressing non-cognitive symptoms such as hallucinations, abnormal beliefs, affective symptoms as well as changes in behaviour, sleep or motor activity at some point in their illness (Lyketsos et al., 2000, Lyketsos et al., 2002). Alzheimer's disease (AD) is the most common cause of dementia, responsible for, or contributing to up to 70% of all dementia cases in the United States (Ehrenberg et al., 2018). People on average live 8-10 years with the condition, but the preclinical disease develops for 10-20 years before the onset of symptoms (Masters et al., 2015). Dementia leads to loss of independence in a person affected by it, carer burden and substantial costs related to formal and informal care (Fiest et al., 2016).

Despite ongoing research into biomarkers for early diagnosis of AD, the identification of patients who will rapidly develop difficulties in activities of daily living, or those who are likely to present with neuropsychiatric symptoms, remains a challenge for clinicians.

1.1 Clinical presentation of Alzheimer's dementia

AD is a neurodegenerative disorder affecting all areas of the brain and causing progressive changes in cognition, everyday functioning and behaviour. People with AD dementia meet the criteria for the diagnosis of all-cause dementia - these include impairment in cognition and behaviour in two or more domains as well as a decline from previous levels in the ability to function at work and everyday life, which cannot be explained by delirium or a major psychiatric disorder (McKhann et al., 2011). In most cases of AD, people will primarily experience difficulties with episodic memory, followed by impairment in planning and sequencing of activities, disorientation in time and space and visuospatial problems. The most common amnestic presentation encompasses deficits in learning new information and in recall of recently acquired knowledge. The less common non-amnestic presentation may involve prominent deficits in the use of language (e.g. logopenic form),

visuospatial skills, or executive functioning (McKhann et al., 2011). Impairment in the ability to perform activities of daily living is essential to make a diagnosis of dementia. The ability to perform activities of daily living - both instrumental, such as managing finances, shopping or household chores, as well as basic self-care activities such as washing and dressing - is important for people with dementia and their carers. An impairment in these domains is linked to increased carer burden and depression (Andersen et al., 2004), though not directly to reduced quality of life (Banerjee et al., 2009).

People with AD dementia typically experience difficulties with operating household appliances and technology as compared to their premorbid level of function, followed by changes to their ability to drive a car, manage bills and finances, handle money and use public transport (Lilamand et al., 2018). Difficulties with preparing meals, choosing clothes and getting dressed, as well as managing personal care, may appear later on with the progression of the condition. There is a relationship between the decline in cognition and the onset and progression in ADL impairment; however, it is not always linear and straightforward. Education level appears to have an impact on performance on tests of cognitive ability but less so on ADL measures, which may be one of the factors explaining the variability (de Oliveira et al., 2015). Measures of executive functioning and visuo-constructive ability are found to be more closely correlated with change on ADL measures (Saari et al, 2018).

Neuropsychiatric symptoms affect most people with AD dementia at some point in the course of the condition and include depression and anxiety, apathy, agitation, as well as psychotic features such as delusional thoughts or hallucinations (Apostolova and Cummings, 2008).

There is no cure for AD, although the first potentially disease modifying anti-amyloid monoclonal antibody, adecanumab, was licensed in the United States by the Food and Drug Agency (FDA) in 2021 (Selkoe, 2021). Adecanumab has been shown to engage the target - i.e. it has led to the clearance of amyloid plaques from the brain. However, the results from two phase-III trials were conflicting and the definitive clinical benefit is yet to be demonstrated (Knopman et al., 2021, Budd Haeberlein et al., 2022). Existing symptomatic therapies, such as acetylcholinesterase inhibitors and memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, have been demonstrated to be

moderately effective in maintaining cognitive and general functioning (Birks, 2006, Winblad et al., 2007, Howard et al., 2012, Birks et al., 2015, Knapp et al., 2017), but not in improving neuropsychiatric symptoms such as agitation in AD (Howard et al., 2007).

1.2 Pathology of Alzheimer's disease and its involvement in cognitive and neuropsychiatric symptoms

The pathological process of AD involves deposition of extra-cellular, misfolded β amyloid protein (Aβ) in the form of plaques, intracellular inclusions of neurofibrillary tangles (NFT) that consist of aggregates of hyperphosphorylated tau protein as well as inflammation (Grundke-Iqbal et al., 1986, Kempf et al., 1996, Ingelsson et al., 2004). Tau protein is essential for efficient functioning of the neurons through its role in the stabilisation of microtubules. Excessive phosphorylation of tau taking place in AD causes its detachment from the microtubule and aggregation in the form of paired helical filaments, which leads to cell dysfunction and ultimately cell death (Scheltens et al., 2016). Neuronal loss, particularly in cholinergic nuclei, causes neurochemical dysfunction that leads to the emergence of cognitive and neuropsychiatric symptoms (Francis et al., 2010). Aβ and tau have a complex relationship to the specific clinical presentation or the severity of AD. Based on neuropathological, and more recently imaging studies, tau pathology corresponds better than Aβ to the stages of AD dementia, whilst it is clear that both pathologies are present for decades before any clinical symptoms may appear (Jones et al., 2017, Maass et al., 2017, Schwarz et al., 2018). Amyloid burden in cognitively normal older people is, however, associated with poorer performance in instrumental ADL (IADL) (Lilamand et al., 2016).

1.3 Diagnosis of Alzheimer's disease dementia

A diagnosis of AD dementia is typically made on the basis of clinical assessment, though the most recent research criteria allow for the diagnosis to be based on biomarkers of Aβ deposition and neuronal injury (McKhann et al., 2011, Dubois et al., 2014). A probable diagnosis of AD dementia can be made when a patient meets the criteria for all-cause dementia, with insidious onset and a clear-cut history of worsening of cognition. The cognitive deficits are usually seen in the domain of episodic memory in the most typical amnestic presentation but

may also present in other cognitive areas. The diagnosis of probable AD may be strengthened in case of decline documented through subsequent assessments or through the evidence of carrier-status of a known causative genetic mutation in amyloid precursor protein (APP) or presenilin 1 (PSEN1) and 2 (PSEN2) genes (McKhann et al., 2011).

The progress in understanding the disease mechanisms as well as developments in brain imaging techniques led to the revision of 1984 National Institute for Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria (McKhann et al., 1984). This allows for incorporation of biomarkers, such as the presence of amyloidosis, evidenced by cerebrospinal fluid (CSF) assay and/or positron-emission tomography (PET) imaging, and neuronal injury that can be established using a proxy of hippocampal volume loss on structural brain imaging, reduced regional brain metabolism detected by PET or through increased level of tau protein in CSF (Dubois et al., 2007, Dubois et al., 2014).

Aetiologically mixed presentation as defined by McKhann's National Institute of Aging - Alzheimer's Association (NIA-AA) criteria meets all core criteria for AD dementia but also involves evidence of other brain pathologies like cerebrovascular disease or features of other neurodegenerative conditions like dementia with Lewy bodies (DLB), or any other neurological or medical comorbidity that may affect cognitive functioning. The presence of multiple pathologies in brains of older people with and without cognitive impairment is being increasingly recognised as it may have an impact on clinical presentation, including neuropsychiatric symptoms, and possibly the response to disease modifying treatments (Schneider et al., 2007, Nag et al., 2018, Naasan et al., 2021).

The widespread use of biomarkers in the diagnosis of Alzheimer's disease and the increased understanding of prodromal and preclinical stages of biomarker positivity has led to a re-framing of the concept of Alzheimer's disease, moving from considering it purely as a form of dementia to treating it as a biomarker-disease continuum (Jack et al., 2018, Petersen et al., 2021). Individuals with abnormal amyloid status (evidence of excess Aβ on PET scan or reduced levels in the CFS) can fall in any of the 3 main clinical stages of cognitively unimpaired, mild cognitive impairment (MCI) or dementia, or any of 6 stages of severity, where 1-3 characterise the pre-dementia stage and 4-6 increasing dementia severity (Jack et al., 2018).

1.4 Spectrum of severity of Alzheimer's disease and the concept of mild cognitive impairment and subjective cognitive decline

As a progressive, neurodegenerative disorder of insidious onset, AD presents over a spectrum of severity from normal ageing, through very subtle changes in cognition and - sometimes - neuropsychiatric symptoms, followed by the objective impairment in (typically) episodic memory and other higher cortical functions (Krell-Roesch et al., 2016). Even at this stage the patient's general functioning may remain unchanged, meaning that dementia cannot be diagnosed even if clinical (e.g. impairment in episodic memory) and biological (evidence of amyloidosis and neuronal injury) features of AD are present. The concept of MCI was introduced to capture the spectrum of severity between normal cognitive ageing and dementia (Petersen, 2004). The usefulness of the concept can be seen in the identification of the population at risk - incidence of dementia in people with MCI is about 12%, compared to 1-3% of general population (Petersen, 2004). When MCI is understood as an objective impairment in one or more cognitive domains without a significant impact on everyday activities, it is a rather heterogeneous concept. Further characterisation of the type of MCI, e.g. relating to the specific cognitive domain and whether more than one is affected, can improve prognostic prediction further, as the conversion rates to dementia appear higher in the amnestic vs. non-amnestic and in multi-domain vs. single domain MCI (Knopman et al., 2015).

Further exploration of the concept of MCI as prodromal AD was provided in the NIA-AA recommendations published in 2011 to accompany the revision of the diagnostic criteria for AD dementia (Albert et al., 2011). The core clinical criteria for the diagnosis of MCI include concern about a change in cognition reported by a patient or their relatives, or possibly observed by a clinician. There should be evidence of impairment in one or more

cognitive domains, greater than expected considering the person's age and educational background. Whilst this may be present in any of the cognitive domains, people who show impairment in episodic memory are more likely to develop AD dementia in the future. Whilst people with MCI may show some degree of change in their proficiency to perform complex ADL, e.g. management of financial affairs, shopping, or computer skills, there should be no impairment in the management of basic activities of daily living. Finally, as expected, people with MCI cannot meet the criteria for dementia.

It is acknowledged that there are no clear-cut boundaries determining whether someone's functional impairment meets the criteria for dementia or not. A careful clinical consideration, taking into account all factors applying to a particular individual, is needed (Albert et al., 2011).

The research criteria for MCI due to AD incorporate biomarkers, such as the evidence of abnormal deposition of Aβ and tau proteins in the CSF or on PET imaging (Laforce et al., 2018). Brain atrophy, seen on structural MRI, and hypometabolism, which can be imaged through fluorodextroglucose (FDG) PET are downstream measures of neuronal injury. Whilst it is recognised that the amyloid biomarkers are seen before the biomarkers of neuronal injury, disruption in brain networks connectivity precedes the stage where Aβ abnormalities are seen (Chen et al., 2016).

The rate of progression of symptoms in MCI and AD varies greatly between individuals. The concept of cognitive reserve and its role in prevention or delay of onset of dementia has been a subject of numerous studies (Livingston et al., 2017). The prospective Personnes Agees QUID (PAQUID) cohort showed that high education delayed the onset of functional decline - i.e. the impairment in IADL by up to 7 years in highly educated individuals (Amieva et al., 2014).

The spectrum of cognitive change, from normal-for-age cognitive functioning to dementia, includes an intermediate stage in which an individual may develop subjective concern about decline, which is not clearly seen on assessment or corroborated by others. This loosely-defined state of subjective cognitive decline (SCD) has attracted a lot of research interest based on a number of papers suggesting it bears an increased risk of progression to MCI and dementia and therefore may be on the AD continuum. There is controversy about the validity of the diagnostic concept, as this level of cognitive change may have a multifactorial aetiology, including systemic medical and psychiatric co-morbidities, other neurological causes and the effects of medication often taken in this age group (Slot et al., 2018).

1.5 Activities of daily living in Alzheimer's disease and mild cognitive impairment

Impairment in ADL is essential for the diagnosis of all-cause dementia. As in the case of cognition and neuropsychiatric symptoms, functional decline is seen on a continuum across the clinical course of AD. A mild degree of impairment in more complex functional ability is observed in MCI, even though at this stage people are able to perform all the basic ADL independently. (Petersen, 2004, McKhann et al., 2011). Impairment in ADL plays a crucial role in the clinical manifestation of dementia and may have a significant impact on quality of life of patients and on carer burden (Mohamed et al., 2010). Despite this, the natural course of ADL decline is an under-researched area (Delva et al., 2014).

The wide spectrum of functional ability has led to categorising ADL into instrumental and basic ADL. Instrumental ADL are considered more complex than very basic activities (such as self-care). An IADL scale developed by Lawton and Brody in 1969 is still used in clinical and research settings, although since then a number of other instruments have been developed (Lawton and Brody, 1969). Cognitive performance in AD appears to be more closely correlated with IADL rather than basic ADL, possibly because the latter remains intact until the later stages of the disorder (Saari et al., 2018). There is a degree of variability in how specific cognitive domains influence ADL (Arrighi et al., 2013). A stronger correlation has been found between executive and visuospatial items of cognitive tests and ADL performance (Kamiya et al., 2018, Saari et al., 2018). A prospective study in an Italian community-based cohort found an association of multi-morbidity with poorer baseline ADL, in people with and without dementia. In the latter group multi-morbidity accelerated functional, but not cognitive decline (Melis et al., 2013).

Mobility is an important factor influencing everyday functioning and independence and although not dementia specific, it is rated in a number of ADL instruments. Whilst there is a substantial overlap of general frailty and motor dysfunction in conditions like DLB (McKeith et al., 2006), there is an independent association between mobility dysfunction and cognition in other types of dementia but also in AD (Verghese et al., 2002, Stark et al., 2013, Tolea and Galvin, 2016). The ability to transfer (move from one item to another, e.g. from chair to bed) within the home is associated with higher quality of life in people with AD (Barbe et al., 2017).

1.6 Neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment

1.6.1 Overall burden of neuropsychiatric symptoms

Neuropsychiatric symptoms is an umbrella term for the non-cognitive clinical manifestations that may occur throughout the course of AD and other dementias. They incorporate psychotic features such as hallucinations and delusions, affective symptoms such as depression, anxiety, apathy, elation, irritability, behavioural manifestations like agitation, aggression, aberrant motor behaviour, as well as changes in sleep and eating habits. These symptoms, also called behavioural and psychological symptoms of dementia (BPSD), are associated with increased disease burden in patients and carers (Coen et al., 1997), and significantly contribute to decisions to move to institutional care (O'Donnell et al., 1992). High levels of behavioural and psychological distress are strongly correlated with reduced quality of life (Banerjee, 2006). Neuropsychiatric symptoms increase the burden of dementia (Rosenberg et al., 2015), worsen quality of life and carer burden (Karttunen et al., 2011, Ryan et al., 2012, Folquitto et al., 2013) and predict faster progression to severe AD and death (Peters et al., 2015). About two-thirds of people with dementia will experience behavioural and psychological symptoms at any one point (Lyketsos et al., 2000). Whilst there is a tendency to associate these symptoms predominantly with moderate severity of dementia, they may be present in people with mild AD as well as those with MCI or even before the manifestation of any cognitive problems (Hallikainen et al., 2012, Wadsworth et al., 2012, Donovan et al., 2014a, Creese et al., 2020). Moreover, symptoms like apathy and anxiety are associated with poorer global functioning in people with MCI (Wadsworth et al., 2012).

A recent review paper reported high prevalence of neuropsychiatric symptoms - between 35% and 85% - in MCI, with depression, apathy and irritability, anxiety, agitation and sleep problems being the most common ones (Martin and Velayudhan, 2020). Seventy-five percent of people with dementia experience at least one neuropsychiatric symptom, the most frequent being apathy, depression and agitation (Lyketsos et al., 2002). The recognition of the common occurrence of neuropsychiatric symptoms in MCI has led to the establishment of the concept of Mild Behavioural Impairment (MBI) (Taragano et al.,

2008) and to the development of instruments designed specifically to detect and measure neuropsychiatric spectrum in the pre-dementia stage, such as the Mild Behavioral Impairment - Checklist (MBI-C)(Mallo et al., 2018).

Neuropsychiatric symptoms present in the pre-dementia stage are particularly interesting from the perspective of their potential prognostic value related to the risk of conversion from MCI to dementia. A prospective volunteer study showed that the presence of more than one neuropsychiatric symptom precedes the diagnosis of any cognitive disorder in a majority of participants (Wise et al., 2019). Kida and colleagues found depression to increase the risk of conversion from amnestic MCI to AD (Kida et al., 2016). A recent study found that individuals with MCI who also reported affective, hyperactive and psychotic/ other severe neuropsychiatric symptoms had a significantly higher risk of converting to dementia when compared to participants with no or mild neuropsychiatric symptoms burden (Qiu et al., 2022).

1.6.2 Specific neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment

1.6.2.1 Psychosis - delusions and hallucinations

Presence of delusions in the course of Alzheimer's disease has been established since the publication of the first case report of Auguste D. by Alois Alzheimer (Alzheimer, 1906). Just over 40% of people with AD develop psychosis, with delusions being more common than hallucinations - 36% vs 18% (Ropacki and Jeste, 2005). Delusions appear to be associated with poorer ADL in people with AD as compared to cognitively-matched AD patients without delusions (Fischer et al., 2012) and with more rapid cognitive decline (Sweet et al., 2000). Cummings postulated that delusions are influenced by the misinterpretation of environmental cues and misattribution of threat, both resulting from limbic dysfunction (Cummings, 1992). Psychosis in AD represents a distinct phenotype with a genetic basis and high heritability (DeMichele-Sweet and Sweet, 2010). Two main subtypes of delusions have been identified in a review by Reeves and colleagues - 'persecutory' delusions and 'misidentification' phenomena, with the latter linked to a higher neuropathological burden in frontal and limbic regions (Reeves et al., 2012). Naasan and colleagues found that psychosis phenotype may be indicative of an underlying pathology,

with those who have predominantly AD reporting fewer psychotic phenomena than people with Lewy body pathology or those with AD and co-occurring Lewy bodies. Fifty percent of patients with AD pathology and hallucinations also reported delusional ideas, mostly of paranoid nature (Naasan et al., 2021). Psychosis in AD is difficult to manage, with medication being either ineffective or likely to cause adverse effects, although some patients respond to low doses of antipsychotics such as risperidone or aripiprazole, which can be adjusted on an individualised basis (Schneider et al., 2006, Reeves et al., 2021, Ismail et al., 2022).

1.6.2.2 Depression and anxiety

Depression in later life has been associated with a prodrome or an increased risk of developing dementia (Agüera-Ortiz et al., 2021). Up to 50% of people with AD may develop mild or more severe depressive symptoms (Starkstein et al., 2005). A genome-wide association study detected genetic association between depression and AD indicating a shared genetic basis, whilst further analysis indicated a causal role of depression in AD (Harerimana et al., 2021). Neurobiological mechanisms of depression in AD are likely to be different from depression in a population without dementia, although neuropathological studies have associated it with the loss of noradrenergic neurones in locus coeruleus (LC) and serotonergic cells in raphe nuclei (Lyketsos and Olin, 2002). Even though depression is a frequent and burdensome feature of AD, it does not improve with commonly used and generally effective antidepressants (Banerjee et al., 2013, Orgeta et al., 2017). However, in people with pre-existing mood disorder it may be of benefit to continue or re-start antidepressants (Livingston et al., 2017). Anxiety is common in AD with the estimated pooled prevalence of just under 40% (Zhao et al., 2016). It is often present in the early stages of AD and may become more prevalent as the disease progresses (Patel and Masurkar, 2021). Co-morbid anxiety in the early stages of AD may worsen cognitive performance and adds complexity to making a diagnosis of dementia (Seignourel et al., 2008). Similarly as depression, anxiety can be a risk factor for dementia - a population study revealed threefold increase in risk of dementia in people with clinically significant anxiety, even when controlling for depression (Santabárbara et al., 2019). It can also be a prodromal symptom of AD and increase the risk of conversion from MCI (Mah et al., 2015). White matter hyperintensities have been associated with anxiety (as well as aberrant motor behaviour and night-time disturbance) by Berlow and colleagues, whilst

Mah found an association between apathy and lower grey matter volume in the entorhinal cortex (Berlow et al., 2010, Mah et al., 2015). Both depression and anxiety appear to be correlated with age (Zhao et al., 2016).

1.6.2.3 Apathy

Apathy is one of the most common neuropsychiatric symptoms in AD, with prevalence ranging from 19% to 88%, and the overall pooled prevalence of 49% (Zhao et al., 2016). The impact of apathy is disproportionately focused on the carer (Lyketsos et al., 2002, Apostolova and Cummings, 2008). Apathy, as well as executive dysfunction, has been found to be associated with impairment in ADL in people with mild-to-moderate AD (Boyle et al., 2003). Apathy is highly prevalent across the AD spectrum, including the prodromal stage, though it may have a different neurobiological basis across the disease severity. One study found that apathy was correlated with hypometabolism in parietal regions in earlier stages of AD, whilst an association between apathy and hypometabolism in medial frontal areas was found in later stages of disease severity (Gatchel et al., 2017). There are no licensed treatments for apathy in AD, but a trial of methylphenidate used in a cohort of men with mild AD showed efficacy in improving measures of apathy in participants as well as in lowering carer burden (Padala et al., 2018). A randomised controlled trial (RCT) of methylphenidate in apathy in AD showed superiority vs. placebo in reducing the Neuropsychiatric Inventory (NPI) (Cummings, 1997) apathy item score, but failed to show significant difference on secondary outcome measures of carer dependency and quality of life (Mintzer et al., 2021).

1.6.2.4 Hyperactivity - agitation, irritability, aberrant motor behaviour and disinhibition

Agitation and aggression are common neuropsychiatric symptoms in dementia, including AD, where they range between 11% and 68% with a pooled prevalence of 40% (Lyketsos et al., 2002, Zhao et al., 2016). The prevalence of agitation increases with the severity of dementia and correlates with functional impairment even when controlling for cognitive decline (Senanarong et al., 2004). It contributes to carer burden and lowers patient and carer quality of life (Cohen-Mansfield and Billig, 1986). Irritability may be present across the disease severity, including people with MCI, and has been found to predict metabolic dysfunction in vulnerable brain regions in preclinical AD (Geda et al., 2008, Ng et al., 2017a). The prevalence of aberrant motor behaviour varies substantially between studies,

depending on study setting and the age of participants, with an overall pooled prevalence of 32%, whilst disinhibition has been reported less frequently, with a pooled prevalence of 17% (Zhao et al., 2016)

1.6.2.5 Sleep and appetite

Eating disturbance in dementia is common and covers a wide range of symptoms, from changes in appetite, through eating habits and finally swallowing difficulties. Nearly half of people with mild AD will experience some degree of change in appetite (Kai et al., 2015). A review paper reported prevalence ranging between 11% and 64% (Zhao et al., 2016). Sleep disturbance is present in around 40% of people with AD, with multiple causes including pain as well as other comorbid neuropsychiatric symptoms such as depression or anxiety (Livingston et al., 2019). As is the case with other neuropsychiatric symptoms, there are no effective pharmacological treatments for sleep disorder in AD.

1.6.3 Neuropathological correlates of neuropsychiatric symptoms

There are conflicting reports relating to the relationship between AD pathology (Aβ and tau) and the risk of neuropsychiatric symptoms. In a Canadian cohort, psychosis (delusions and hallucinations) was associated with greater cerebrovascular burden, Lewy body pathology and vascular risk factors (Fischer et al., 2016). Increased Aβ plaques and NFT burden in middle frontal cortex and hippocampus, parahippocampal gyrus and entorhinal cortex were found in patients with misidentification phenomena (Reeves et al., 2012).

Higher Aβ burden, as measured by Pittsburgh compound B (PiB) PET, predicted worsening on Geriatric Depression Scale (GDS) in preclinical AD, suggesting anxiety and depression may be prodromal symptoms of AD dementia (Donovan et al., 2018). Conversely, a study performed on an autopsy sample of cases with AD pathology revealed an association between the presence of neuropsychiatric symptoms dependent on tau pathology as measured by Braak staging. Agitation, depression, anxiety, appetite changes and sleep disturbance was associated with states I/II, whilst increased odds for agitation continued through all Braak stages I - VI. However, there was no association with Aβ burden measured by Consortium to Establish a Registry for AD (CERAD) neuropathology

protocol score (Mirra et al., 1991, Ehrenberg et al., 2018). Banning and colleagues also reported on two cohort studies of patients with AD and MCI, where there was no association between CSF levels of Aβ, total and phospho-tau or hippocampal volume and depression, agitation, irritability and sleep disturbance, but lower levels of Aβ and smaller hippocampal volumes were associated with anxiety. However, this association was influenced by the degree of cognitive impairment (Banning et al., 2020). Data from a study looking at the relationship between neuropsychiatric symptoms and co-morbid pathologies in participants with AD found that anxiety, irritability, sleep behaviour and appetite problems were associated with the presence of Lewy bodies, whereas transactive response deoxyribonucleic acid binding protein 43 (TDP-43) was associated with aberrant motor behaviour (Bayram et al., 2019).

1.6.4 The unique nature of neuropsychiatric symptoms in Alzheimer's disease - a summary

Neuropsychiatric symptoms in AD, and more generally in neurodegenerative disorders, appear to have different biological background when compared to similar symptoms experienced by people without dementia - for example, they respond differently to treatment (Banerjee et al., 2013). Rather than being only a consequence of cognitive and functional decline, or an individual's reaction to the perceived deficits, neuropsychiatric symptoms are present across the severity of AD including preclinical and prodromal stages. Their relationship to neuropathology of AD and any co-morbid proteinopathies is complex, as is their association with changes in brain structure and function. Therapeutic approaches to neuropsychiatric symptoms are of great importance due to their attributable disease burden. It is clear that treatment should be targeted at specific symptoms and its risks and benefits considered very carefully (Ballard et al., 2015, Livingston et al., 2017, Livingston et al., 2020).

1.7 Neuroimaging in Alzheimer's disease and mild cognitive impairment

1.7.1 Neuroimaging in the diagnosis and prognosis of Alzheimer disease

Magnetic resonance imaging (MRI) and other imaging techniques, such as computed tomography (CT), are used routinely and widely in clinical settings, mainly to aid making a diagnosis or to monitor disease progression. In research settings, the MRI techniques most widely used to characterise AD include:

- volumetric MRI - 3D representation of brain structure, which allows to use methods such as voxel-based morphometry (VBM) to measure whole the volume of the whole brain, or its particular structures such as medial temporal lobe, hippocampus or entorhinal cortex (Kesslak et al., 1991, Jack et al., 1997, Ashburner and Friston, 2000)

- functional MRI (fMRI) - imaging of activation in the brain, which can be studied in a designed paradigm to visualise event-related brain activation (Josephs et al., 1997, Friston et al., 1998); or at rest (resting-state functional MRI - rs-fMRI) to visualise spontaneous, synchronous brain activity in various brain regions, reflecting functional connectivity within large-scale brain networks (Friston, 1994, van den Heuvel and Hulshoff Pol, 2010)

- diffusion MRI - a technique that probes tissue microstructure and white matter connections (Bozzali et al., 2001).

Volumetric and functional MRI, including functional connectivity, are further described in chapter 2.

The application of MRI to predict the conversion from MCI to AD is of particular interest, both in terms of ascertaining the risk as well as in identification of population at risk that would be eligible for potential disease modifying treatment. Automatic classification software uses pattern recognition to objectively classify subjects to a particular group. It has been used in various protocols, including identification of conversion from normal elderly cognition to AD with the use of multimodal support vector machine (SVM) (Zhan et al., 2015). More recently a different machine learning protocol was used to determine both the subtype and stage in frontotemporal dementia (FTD) and AD (Young et al., 2018).

Another study used grey matter (GM) volume in the hippocampus and parahippocampal gyrus, as well as specific regions of interest (ROI), in identifying people with AD at the stage of MCI, thus helping early diagnosis (Guo et al., 2014). Khazaee and colleagues showed that a combination of automatic classification and graph theory methods of analysis of resting-state functional MRI (rs-fMRI) may help distinguish healthy volunteers from people with MCI and AD (Khazaee et al., 2016).

AD has been postulated to be a disconnection syndrome with evidence from neuropathological, electrophysiological and neuroimaging data (Delbeuck et al., 2003). This prompted adoption of the approach of network analysis to explore the pathological processes in this condition. One way of characterising brain networks relies on measuring the functional connectivity between segregated areas of the brain at rest. In this way intrinsic resting state networks can be seen as modules - clusters of network nodes with many connections between its nodes, and less dense connections with other clusters. This characteristic is named network modularity. The density of between-node connections within a cluster, or a module, and the loose connections with other modules also reflect network segregation, i.e. the ability to distinguish between two separate brain network (Contreras et al., 2019). The relationship between and within networks changes over the life span, with network segregation increasing in healthy ageing (Chan et al., 2014). In a study comparing healthy volunteers, people with SCD, aMCI and AD, the frontoparietal network showed greater internal coherence and stronger coupling with the default mode network (DMN), which led to reduced segregation between them (Contreras et al., 2019).

Recently there have been efforts to combine and integrate conventional structural MRI with resting state functional MRI (rs-fMRI), also referred to as functional connectivity, to improve algorithms to predict the conversion risk from MCI to AD (Hojjati et al., 2018). A disconnection between discrete brain regions that function as networks has been previously identified as an early and specific feature in AD (Bozzali et al., 2011). Additionally, a number of functional networks have been postulated as early and specific targets in AD (Rombouts et al., 2005). A recent study carried out in mutation carriers from the Dominantly Inherited Alzheimer Network (DIAN) showed evidence of increased WM diffusivity, a measure of reduced integrity of WM in mutation carriers as compared to family non-carriers, present between 5 to 10 years before the estimated symptom onset

(estimated years to onset - EYO). The earliest increase in diffusivity was observed in long projection fibres connecting to regions of DMN - this study suggests that changes in brain connectivity may occur many years before the onset of symptoms in AD (Araque Caballero et al., 2018).

1.7.2 Neuroimaging correlates of activities of daily living

A number of studies investigated the neural correlates of impairment in cognitive domains in dementia (Leyton et al., 2017, Epelbaum et al., 2018). However, the relationship between the risk of developing more rapid impairment in ADL and specific structural or functional features on brain imaging has not been clearly established so far. A cross-sectional study reported by Vidoni and colleagues compared people with early AD and healthy volunteers whilst exploring the relationship between cognition, physical function and functional independence, using mediation and correlation analysis. The study revealed that cognitive impairment had a direct effect on independence and also mediated the influence of physical function on independence in subjects with AD. A voxel-based morphometry (VBM) analysis found that atrophy in medial frontal and temporo-parietal areas was correlated to impairment in all three clinical variables (Vidoni et al., 2010).

A study performed on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, including participants with amnestic MCI (aMCI), AD and healthy volunteers, explored whether hippocampal atrophy was associated with impaired IADL. The study found that pre-defined hippocampal volume (derived from adding left and right hippocampal volumes) in the functionally unchanged participants was larger when compared to subjects with moderate-to-severe level of IADL impairment, although baseline cognition was not controlled for. The hippocampal volume of subjects with a mild degree of functional impairment was larger when compared with moderately to severely impaired groups although this difference did not survive the correction for multiple comparisons (Brown et al., 2011).

Neural correlates of functional decline may vary between specific disorders. Mioshi and colleagues compared neuroimaging correlates of ADL in 52 participants with various subtypes of frontotemporal lobar degeneration (FTLD), 20 subjects with AD and 18 healthy volunteers. A whole-brain VBM analysis was used to explore between-group differences

and correlation with ADL. The results showed that ADL impairment in participants with FTLD was associated with prefrontal and thalamic atrophy, whilst a wide-spread atrophy including temporal, parietal and frontal areas as well as the basal ganglia (caudate) correlated with functional decline in people with AD (Mioshi et al., 2013).

Another VBM study explored the neuroanatomy of a spectrum of ADL, ranging from basic to advanced (required for complex interpersonal or social functioning) (Slachevsky et al., 2019). The researchers compared 33 participants with a clinical diagnosis of AD and 30 healthy volunteers. Basic ADL dysfunction correlated with frontal atrophy, IADL with more widespread frontal, occipital and temporal volume loss and the performance on ADL related to information and communication technologies (ICT) correlated with brain volume in the precuneus. The authors used masking to explore the overlap between anatomical regions of brain atrophy that accounted for functional impairment in various ADL domains. They found that cortical volume loss correlating with basic ADL did not overlap with either instrumental or advanced ADL, which both correlated with atrophy in the regions of bilateral parahippocampal gyrus, right precuneus, left paracingulate gyrus and left intracalcarine cortex. The reported results were uncorrected at $p<0.001$ and included clusters with at least 100 contiguous voxels.' (Slachevsky et al., 2019).

Nadkarni and colleagues used single-proton emission computed tomography (SPECT) to study a cross-sectional relationship between IADL in 121 patients with mild AD and 42 age-matched healthy controls. A priori ROIs were specified in limbic and association cortex including frontal pole, prefrontal cortex, cingulate cortex, temporal pole and temporal medial and lateral cortex, superior and inferior parietal cortex, basal ganglia, thalamus and occipital cortex. All AD participants had lower perfusion ratios in all ROIs, with the biggest difference between groups in anterior and posterior cingulate and parietal areas bilaterally. Correlation analysis with IADL found a negative correlation between performance on instrumental ADL and perfusion in right temporo-parietal regions in an exploratory study using 13 ROIs in people with mild AD. However, the study did not correct for multiple comparisons and had a relatively small study sample considering the number of correlations performed (Nadkarni et al., 2012).

Mobility is a specific domain of ADL and as such is included in measures of ADL such as the Bristol Activities of Daily Living scale (BADLS, used in this study) (Bucks et al.,

1996). A recent study explored the relationship between the 'timed up and go' (TUG) test, a measure of mobility, and structural differences in the regional GM in healthy volunteers and subjects with MCI. GM volume in distinct brain regions was inversely correlated with TUG: right inferior frontal gyrus (IFG) in healthy volunteers and bilateral cerebellum and left middle cingulate cortex in MCI. A further GM covariance analysis (using right IFG as a seed region) revealed associations with brain regions mapping onto the nodes of DMN in healthy volunteers, whilst for the MCI group the seed regions included lobule VIII in the left cerebellum, which covaried with other cerebellar regions, as well as frontal and temporo-parietal regions. However, no functional MRI (fMRI) connectivity analysis was performed in this study (Allali et al., 2020).

Marshall and colleagues explored the relationship between IADL, regional cortical thinning and AD biomarkers in the CSF in cognitively unimpaired volunteers, subjects with MCI and those with AD. Participants had baseline MRI and CSF analysis as well as annual clinical assessment for at least 3 years. The study protocol specified seven ROI in temporal, parietal, cingulate, prefrontal and lateral occipital cortices. The results of a baseline cross-sectional analysis suggested that lower inferior temporal cortical thickness and higher levels of CSF Aβ were associated with greater IADL impairment in mild AD, whilst baseline lower lateral parietal and inferior temporal cortical thickness, as well as lower Aβ and higher total tau in the CSF were associated with worsening IADL over time in all three groups (Marshall et al., 2014). Whilst this study addresses the predictive value of imaging in ADL prognosis in AD, the ADNI-derived study population is not necessarily representative of community samples (Weiner et al., 2012).

Molecular imaging techniques, such as FDG PET have also been used to study the relationship between biomarkers, including the imaging ones, and ADL in AD. Robb and colleagues found that baseline imaging biomarkers such as mean FDG count and CSF Aβ levels correlate significantly with a change in IADL over a 3 year period in a cohort with MCI (Robb et al., 2017). Previously, Melrose and colleagues used FDG PET and VBM to explore brain regions associated with decline in IADL. The study found an association between poorer ability to perform IADL and hypometabolism in right-sided areas of parietal lobe, posterior temporal cortex, dorsolateral prefrontal cortex (DLPFC) and frontal pole. The association was further tested using multiple regression with MMSE score as

a mediator (Baron and Kenny, 1986) - the results showed that the association between hypometabolism in the frontal, but not so much in parietal areas, was substantially attenuated by cognitive score (Melrose et al., 2011).

A summary of brain regions implicated in ADL dysfunction is presented in Table 1.

Table 1. Neural correlates of activities of daily living in Alzheimer's disease and mild cognitive impairment

Study	**ADL**	**Imaging technique**	**Findings**
Vidoni et al., 2010	Independence	MRI	Reduced volume in medial frontal and temporo-parietal cortex
Brown et al., 2011	IADL	MRI	Reduced hippocampal volume
Marshall et al., 2014	IADL	MRI	Cortical thinning in lateral parietal and inferior temporal cortex at baseline
Mioshi et al., 2013	ADL	MRI	Atrophy in temporal, parietal, frontal areas and caudate nucleus
Robb et al., 2017	IADL	FDG-PET	FDG-PET hypometabolism and CSF Aβ predict functional impairment at 3 year follow-up
Nadkarni et al., 2012	IADL	SPECT	Reduced perfusion in PCC and parietal areas
Melrose et al., 2011	IADL	FDG-PET	Hypometabolism in R-sided cortex
Slachevsky et al., 2019	aADL	MRI (VBM)	Basic ADL - frontal atrophy, IADL - frontal, temporal and occipital atrophy

ADL - activities of daily living, MRI - magnetic resonance imaging, IADL - instrumental activities of daily living, MRI - magnetic resonance imaging, FDG-PET fluorodextroglucose positron emission tomography, CSF - cerebrospinal fluid, Aβ - amyloid beta, SPECT - single proton emission computed tomography, aADL - advanced activities of daily living, VBM - voxel based morphometry

Studies using cross-sectional design and relatively small numbers of participants do not

allow us to draw conclusions that implicate brain regions in being closely associated with, or predictive of, functional impairment in AD. Those that repeated clinical assessment over time to study the predictive values of imaging markers, often used pre-specified ROI analyses.

1.7.3 Neuroimaging correlates of neuropsychiatric symptoms

The association of neuropsychiatric symptoms with specific neuroanatomical structures and networks has been studied using structural and functional MRI, CT, as well as molecular imaging like SPECT or PET (Boublay et al., 2016). More recently, machine learning (ML) techniques have included neuropsychiatric symptoms in the models predicting follow-up diagnoses in people with cognitive dysfunction in combination with neuroimaging findings. One study reported on a ML model that required only two features - left hippocampal volume and total MBI score (Gill et al., 2020) to predict conversion to dementia. However, to our knowledge there have been no studies using ML applied to brain imaging to predict the risk or severity of neuropsychiatric symptoms in the future.

A number of volumetric studies, using structural MRI to explore neural correlates of neuropsychiatric symptoms used either a pre-specified ROI or a whole-brain analysis. The publications mostly report on cross-sectional correlations, though there have been studies that included follow-up measures of clinical variables. In one of those, agitation and aggression in a sample of participants with MCI and AD was inversely correlated with regional brain volume in pre-specified ROI in frontal, insular, and cingulate cortices as well as in the hippocampus and amygdala (Trzepacz et al., 2013). More recently Boublay and colleagues reported on a cohort of 53 participants with AD whose neuropsychiatric assessment was repeated 6-monthly over the period of 18 months. VBM analysis comparing the group of patients with AD and 40 healthy volunteers from the ADNI database suggested that volume loss in many brain regions, involving frontal, temporal, parietal and occipital areas as well as the cerebellum and some subcortical structures was associated with higher risk of neuropsychiatric symptoms. The clusters in frontal regions, such as the anterior cingulate cortex (ACC) and the insula, were strongly predictive of neuropsychiatric symptoms. The results were not corrected for multiple comparisons, but adopted a threshold of 100 contiguous voxels to report significance (Boublay et al., 2020).

New MRI sequences, such as neuromelanin - sensitive MRI (NM-MRI) can be used to assess the integrity of LC, which is a noradrenergic nucleus affected early in the AD process (Jacobs et al., 2021). There is correlation between the noradrenergic system, hyperphosphorylated tau burden and disease progression in AD (Gannon and Wang, 2019), but a recent study found that the preserved integrity of LC may increase the risk of impulse-control symptoms in AD, raising the possibility of using measures of LC integrity to inform the prediction of risk of NPS in this condition (Cassidy et al., 2022).

1.7.3.1 Multiple neuropsychiatric symptoms

A number of studies explored neural correlates of multiple neuropsychiatric symptoms, usually measured by NPI. Bruen and colleagues reported on neuroanatomical correlation of neuropsychiatric symptoms in AD in a cross-sectional VBM study of 31 patients with mild AD (Bruen et al., 2008). Their findings revealed that GM volume in left insular and bilateral ACC correlated negatively with the severity of aggression and agitation. Delusions were associated with decreased GM volume in left frontal, left claustrum and right frontoparietal cortex, whereas the severity of apathy correlated with decreased GM volume in ACC and frontal cortex bilaterally, as well as in the left head of caudate and in the left and right putamen. The authors postulated that neuropsychiatric symptoms correlate with disruption of brain circuits involved in personal memory, reality monitoring, reward system and interoceptive sensation (Bruen et al., 2008). Makovac and colleagues identified the relationship between white matter damage in the corpus callosum and GM atrophy and clusters of neuropsychiatric symptoms such as mood, frontal symptoms, psychosis and the overall neuropsychiatric burden (Makovac et al., 2016).

Jaramillo-Jimenez and colleagues adopted a prospective approach to observe how baseline volume of the amygdala influenced the risk of developing neuropsychiatric symptoms in patients with AD and DLB (Jaramillo-Jimenez et al., 2021). The study revealed a negative correlation between the amygdala volume and the risk of developing agitation and aggression, but a positive correlation with the risk of depressive symptoms over the 5-year period in participants with AD (Jaramillo-Jimenez et al., 2021).

1.7.3.2 Apathy

There have been replicated reports implicating an association between apathy and

atrophy, and reduced glucose metabolism or hypoperfusion in frontal areas such as prefrontal cortex, ACC and insula (Marshall et al., 2007, Bruen et al., 2008, Boublay et al., 2016, Kazui et al., 2017). The ACC link was also confirmed in a review by Raimo and colleagues, who reported an association between apathy and the reduced perfusion and GM volume in ACC in AD patients (Raimo et al., 2018).

Some studies have found regional brain differences in subcortical structures such as the basal ganglia or thalamus (Kazui et al., 2017, Jeong et al., 2018). Torso and colleagues investigated white matter lesions (WML) and their impact on neuropsychiatric symptoms in patients with aMCI. They reported a strong association between apathy, but not other symptoms, and the presence of white matter (WM) lesions in the region of anterior thalamic radiation, suggesting that disconnection between thalamus and prefrontal areas may have a role in pathophysiology of apathy in this clinical population (Torso et al., 2015). Moreover, alterations in white matter microstructure, as measured by DTI, were also associated with apathy in aMCI in a study that reported increased mean diffusivity correlated with apathy in the uncinate, middle longitudinal and inferior longitudinal fasciculi and in parathalamic WM, the fornix and the posterior cingulum, whilst fractional anisotropy was reduced in almost all WM areas (Cacciari et al., 2010).

Reduced glucose metabolism in ACC extending to medial orbitofrontal cortex (OFC) areas was linked with apathy in patients with AD (Marshall et al., 2007).

Kumfor and colleagues studied apathy in 53 patients with AD and 69 patients with behavioural variant frontotemporal dementia (bvFTD), applying a multidimensional model recognising affective, behavioural and cognitive components of apathy. In their study, whilst participants with bvFTD had high degrees of affective and cognitive apathy, both higher than behavioural type, there was no significant difference between the two of them. Neuroimaging results of this study suggest distinct neural correlates of the three apathy types. Cognitive apathy was inversely correlated with regional GM intensity in the left OFC and subcallosal regions, medial prefrontal cortex, ACC, superior frontal gyrus (SFG), inferior temporal gyrus (ITG) and PCC, whilst affective apathy correlated with lower GM intensity in the left temporal pole, bilateral OFC, subcallosal cortex and insula. Behavioural apathy was inversely correlated with GM intensity in frontal pole, subcortical areas and the cerebellum in patients with AD had significantly higher cognitive apathy than behavioural or

affective (Kumfor et al., 2018). A similarly designed study with 42 participants with bvFTD, 42 with AD and a group of 30 healthy volunteers explored neural correlates of apathy on FDG-PET imaging. This study reported distinct correlates of apathy in two patient groups with hypometabolism in the left lateral prefrontal, medial frontal/ACC, lateral OFC and anterior insular areas in bvFTD and in the right ACC in AD (Fernández-Matarrubia et al., 2018).

Jeong and colleagues reported findings of a study using another molecular imaging method - brain perfusion SPECT - to explore differences in regional cerebral blood flow (rCBF) in people with apathy in AD as compared to patients with AD and no apathy. Participants with apathy showed reduced rCBF in the bilateral OFC, left putamen, left nucleus accumbens, left thalamus and bilateral insula when compared to apathy-free participants. Additionally, there was inverse correlation between the severity of apathy as measured by NPI apathy score and mean perfusion in the above regions (Jeong et al., 2018). However, a more recent study of regional perfusion in apathy that used an automated Brodmann areas (BA) analysis in patients with FTD and AD showed significant overlap between apathy correlates in prefrontal areas and ACC. There were, however, group differences such as reduced perfusion in occipital areas in AD and in temporal areas in FTD (Valotassiou et al., 2022).

Kazui and colleagues explored neural correlates of apathy in patients with aMCI using VBM and SPECT imaging. In patients who had SPECT-imaging features indicative of an underlying AD, apathy was inversely correlated with GM volume in the right caudate nucleus and with the reduction in rCBF in frontal, inferior temporal and occipital areas (Kazui et al., 2017). Bruen and colleagues used a VBM approach to explore correlates of neuropsychiatric symptoms as measured by NPI in 31 patients with mild AD. This study found that apathy was associated with atrophy in in ACC, OFC and DLPFC (Bruen et al., 2008).

1.7.3.3 Hyperactivity symptoms

Gill and colleagues explored the prevalence of impulse dyscontrol syndrome, which includes aggression and agitation, and its association with regional GM volume and WM integrity in people with MCI, AD and healthy volunteers (Gill et al., 2021). Dyscontrol

syndrome was present in 43% of participants with MCI and 66% of subjects with AD. WM integrity was measured by fractional anisotropy and radial diffusivity in diffusion tensor imaging (DTI) (Gill et al., 2021).

Molecular imaging techniques, such as perfusion SPECT or FDG-PET have been used to study neural correlates of agitation and aggression in AD. Glucose hypometabolism in frontal and temporal cortex appears to be associated with agitation and disinhibition (Sultzer et al., 1995). A more recent study found a correlation between agitation and irritability scores and hypometabolism in right frontal and temporal cortex and bilateral cingulate (Weissberger et al., 2017). Banno and colleagues divided agitated behaviour into three dimensions, including psychosis as well as physical and verbal agitation. Physical agitation was associated with reduced rCBF in the right superior temporal gyrus (STG) and the right inferior frontal gyrus (IFG). Verbal agitation was inversely correlated with rCBF in the left IFG and the left insula (Banno et al., 2014).

1.7.3.4 Psychosis

Nomura and colleagues explored neural correlates of delusions in AD by classifying them into three groups of factors and applying perfusion SPECT imaging techniques (Nomura et al., 2012). The study reported distinct and complex patterns of hypo- and hyperperfusion, depending on the sub-type of delusional beliefs and mapping onto distinct brain regions. Factor 1 included delusions of misidentification of place or person, phantom boarder beliefs and delusions of abandonment. This group of symptoms was associated with hypoperfusion in the right temporal lobe and medial frontal/precentral areas. Factor 2 included beliefs that people from television were communicating with the subject and persecutory beliefs - these symptoms were associated with hypoperfusion in the precuneus and hyperperfusion in the insula and thalamus. Finally, factor 3 beliefs that consisted of feelings of abandonment and delusional jealousy correlated with hypoperfusion in the right inferior temporal and frontal areas and hyperperfusion in the middle frontal gyrus (MFG). Additionally, delusions of theft, which did not appear to load into any of the three factors, were associated with hypoperfusion in the bilateral thalami and left PCC, as well as hyperperfusion in the left IFG and ACC (Nomura et al., 2012). A similar approach of separating psychotic symptoms by sub-types of misidentification phenomena and paranoid beliefs was adopted by Lee and colleagues (Lee et al., 2016). In

their study 40 patients with AD and psychosis and 25 participants with AD but no psychotic symptoms underwent a structural volumetric MRI. The images were analysed by VBM and revealed distinct pattern of atrophy depending on the subtype of psychotic symptoms. Patients with misidentification had more atrophy in the right hemisphere as compared to psychosis-free participants. Patients with paranoid beliefs however had less atrophy in the frontal, temporal and parietal areas when compared with participants with no psychosis (Lee et al., 2016). In a cerebral perfusion study that considered psychosis as one of three dimensions of agitated behaviour in AD, an association between psychosis and hypoperfusion in the right angular gyrus and in the right occipital lobe was found (Banno et al., 2014).

1.7.3.5 Affective symptoms

A study investigating anxiety in AD with SPECT and volumetric MRI found a correlation between anxiety scores and hyperperfusion in ACC and reduced GM volume in the inferior parietal lobule (Tagai et al., 2014). Hyperperfusion in the right supramarginal gyrus (SMG) and right supplementary motor area was also found in a study using arterial spin labelling technique (ASL) (Li et al., 2021a). However, hypoperfusion in frontal areas such as the superior and middle frontal gyri was found in an earlier study, although when correcting for atrophy the difference between patients with and without depression was no longer significant (Levy-Cooperman et al., 2008). Similar association between depressive symptoms and reduced perfusion in inferior frontal areas were found by Honda and colleagues in a group of 67 patients with AD (Honda et al., 2014). Wu and colleagues explored the relationship between depression symptoms measured by Hamilton Depression Rating Scale (HDRS) and GM volume in patients with AD and healthy volunteers. They found an inverse correlation between HDRS and GM volume in the insula (Wu et al., 2020).

1.7.3.6 Sleep and appetite

Sleep and appetite have been included with other neuropsychiatric symptoms as reported earlier. Matsuoka and colleagues explored neural correlates of sleep disturbance in a study of 63 patients with AD, comparing participants with and without sleep disorder (Matsuoka et al., 2018). Participants with sleep disturbance had significantly smaller GM volume in precuneus, a region that is involved in DMN and whose connectivity has been

shown to be reduced post sleep deprivation (Wu et al., 2021). A study exploring rCBF in AD patients with sleep disorder found differences in perfusion between groups with decreased perfusion in the frontal and temporal areas and increased perfusion in parietal regions (including precuneus) as well as occipital lobe and in participants with sleep disturbance (Im et al., 2017).

1.7.3.7 Resting state connectivity and neuropsychiatric symptoms

Resting state fMRI (rs-fMRI) offers the opportunity of studying the intrinsic functional connectivity of the brain at rest, which is an attractive option to use in participants with dementia as subject engagement in a task is not required. Whilst changes in brain networks such as DMN have been observed consistently in people with AD, including those in prodromal phase (Greicius et al., 2004, Seeley et al., 2009), the relationship between neuropsychiatric symptoms and alteration in resting state connectivity has not been explored extensively.

One of the first studies to explore the relationship between resting state networks and neuropsychiatric symptoms was carried out by Balthazar and colleagues (Balthazar et al., 2014). The project included 20 patients with mild AD and 17 healthy volunteers, whose neuropsychiatric symptoms were measured by the NPI (Cummings, 1997). The association of NPI sub-syndromes of Apathy, Affective symptoms, Hyperactivity and Psychosis with connectivity within the default mode and salience networks was analysed. The results revealed a positive correlation with Hyperactivity in the regions of the anterior salience network, including the right ACC and the right insula. There was no significant correlation between other sub-syndromes and the salience and default mode networks activity following correction for atrophy and multiple comparisons (Balthazar et al., 2014).

Munro and colleagues studied resting state functional connectivity in 42 participants with aMCI, focusing on DMN, frontoparietal control network and dorsal and ventral attention networks. The results showed an inverse correlation between the Affective (but not the Hyperactivity) sub-syndrome and connectivity in frontoparietal control network. Additionally, the single item of apathy was associated with reduced connectivity within the same network (Munro et al., 2015).

Guo and colleagues studied the relationship between depression and functional connectivity in 21 depressed and 21 non-depressed patients with AD. Functional connectivity was explored by using the amygdala as the seed region. The results showed an increase in functional connectivity between the amygdala and the OFC, as well as the reduction in connectivity with medial prefrontal cortex and IFG in depressed participants when compared to the non-depressed group, suggesting an abnormal amygdala - prefrontal connectivity in depression in AD (Guo et al., 2018). Zhang and colleagues, who also studied functional connectivity in depressed vs. non-depressed AD patients found an asymmetrical alteration in functional connectivity of PCC to right-sided amygdala, parahippocampal gyrus, temporal pole, middle temporal lobe and hippocampus (Zhang et al., 2017).

The relationship between depression and resting state connectivity in AD was also explored by adopting a graph theory approach (Guo et al., 2016b). This study used degree centrality, which is a graph-based quantification of network organisation based on a number of connections of a particular region, which reflects its influence. The study used this measurement to identify voxels with altered functional connectivity, followed by a more detailed seed-based analysis of their connectivity patterns. Patients with AD and depression had lower degree centrality values in the right pre-and post-central gyri and in the MFG as compared to participants with no depression. Furthermore, the connectivity between pre- and post-central gyri and the supplementary motor area and middle cingulum was reduced, suggesting a network dysfunction different from patterns observed in AD without depression, or in major depressive disorder, where functional connectivity within the DMN is increased and positively correlated with the length of depressive episode (Greicius et al., 2007, Guo et al., 2016b).

Reduced connectivity between VTM and parahippocampal gyrus and cerebellar vermis correlated with irritability, agitation and disinhibition, whilst disconnection between VTA and striatum as well as insular cortex was linked to increased scores in sleep and eating dysfunction (Serra et al., 2018).

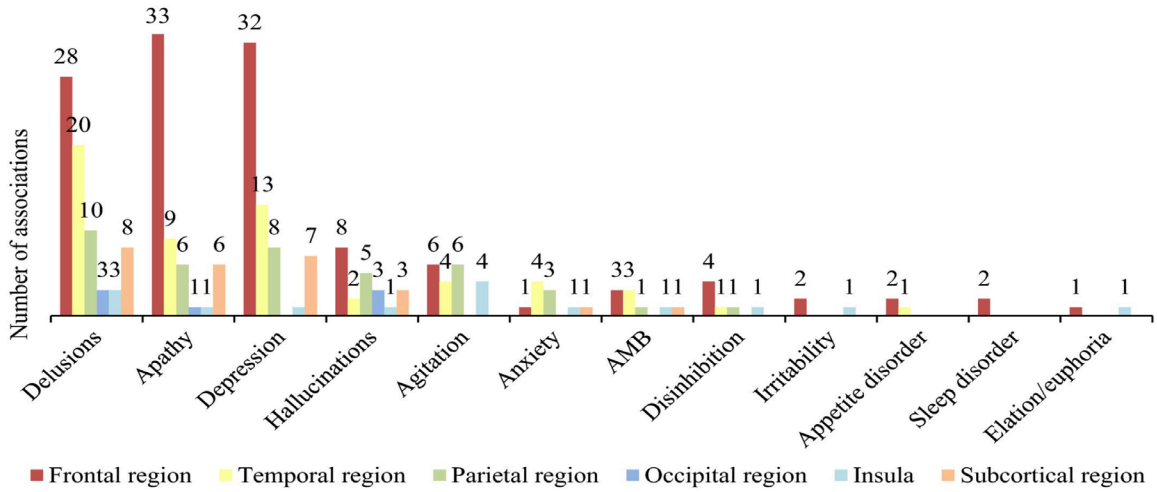
A study based on resting state fMRI explored low-frequency oscillations in patients with AD and depression, as compared to those with AD and no depressive features. Participants with depression showed a varied pattern of change in the amplitude of low frequency

fluctuations (ALFF), with increased values in the caudate and thalamus, but a decrease in ALFF in the frontal pole, all lateralising to the left (Liu et al., 2017). ALFF reflects the intensity of spontaneous fluctuations of the BOLD signal (Wang et al., 2019). Studies have shown reduced ALFF in brain regions in people with aMCI and AD as compared to healthy controls (Cha et al., 2015). A pattern of both increased and decreased AFLL in the basal ganglia and middle frontal gyrus as reported by Liu et al. suggests a complex relationship between brain connectivity and depression in AD, moreover, there was no significant correlation between ALFF and the score on depression scales, though this may be due to a relatively small study sample (Liu et al, 2017).

Qian and colleagues studied differences in connectivity within DMN in patients with and without delusions in the course of AD. In this study, participants with delusions had lower connectivity between the left inferior parietal lobule and other regions of DMN when compared with participants without delusions (Qian et al., 2019).

A comprehensive review of neuroimaging correlates of neuropsychiatric symptoms was published by Boublay and colleagues in 2016. The review summarises the results from 118 studies published between 1990-2015, separating the findings by the 12 neuropsychiatric symptoms as listed in NPI (Cummings, 1997). Figure 1 shows the number of associations between neuropsychiatric symptoms and the main brain regions (Fig.1). In this review, delusions, apathy and depression were the most prevalent symptoms showing the association with brain changes. In contrast, irritability, appetite changes, sleep disturbance and euphoria had the fewest associations with regional brain differences. The most consistent brain region associated with neuropsychiatric symptoms was the frontal lobe, specifically the ACC and orbitofrontal cortex (OFC) - mapping to symptoms such as delusions, apathy, and depression, whereas the insula and the occipital lobe were the least likely to be associated with neuropsychiatric symptoms (Boublay et al., 2016).

Figure 1. Neural correlates of NPS adapted from Boublay et al., 2016



AMB - aberrant motor behavior

A summary of imaging findings exploring the relationship between brain regions and network with neuropsychiatric symptoms is presented in Table 2.

Table 2. Neural correlates of neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment organised per symptom/syndrome.

Study	**NPS**	**Imaging technique**	**Findings**
Banno et al., 2014	Agitated behaviour	SPECT	Psychosis - hypoperfusion in the right angular gyrus and right occipital lobe. Physical agitation: reduced rCBF in the right STG and the right IF. Verbal agitation: reduced rCBF in the left IFG and the left insula.
Trzepacz et al., 2013	Agitation, aggression	MRI (VBM)	Reduced volume in the hippocampus, amygdala and frontal, insular and cingulate cortices was associated with higher severity
Gill et al., 2021	Agitation, aggression and irritability - impulse dyscontrol	MRI (VBM and DTI)	Reduced FA and increased diffusivity in the fornix, superior fronts-occipital fasciculus. Greater diffusivity in the cingulum and uncinate fasciculus. Lower cortical thickness in the parahippocampal gyrus.

Study	NPS	Imaging technique	Findings
Tagai et al., 2014	Anxiety	MRI, SPECT	Hyperperfusion in anterior cingulate cortex and reduced GM volume in inferior parietal lobule
Kumfor et al., 2018	Apathy	MRI (VBM)	Multiple regions in frontal and temporal areas as well as subcortical structures associated with subtypes of apathy
Fernandez-Matarrubia et al., 2018	Apathy	PET	Hypometabolism in right ACC in AD
Jeong et al., 2018	Apathy	SPECT	Hypoperfusion in OFC, striatal and insular regions in AD patients with apathy
Valotassiouu et al., 2022	Apathy	SPECT	Hypoperfusion in prefrontal cortex, ACC and occipital lobe associated with apathy in AD
Kazui et al., 2017	Apathy	MRI (VBM), SPECT	Apathy correlated with reduced GM volume in right caudate and hypoperfusion in rCBF in frontal, inferior temporal and occipital areas
Cacciari et al, 2010	Apathy	MRI (DTI)	Mean diffusivity correlated positively and fractional anisotropy inversely with apathy in multiple WM tracts
Marshall et al., 2007	Apathy	PET	Hypometabolism in OFC and ACC
Raimo et al., 2019	Apathy	MRI, PET	Reduced perfusion and GM volume in ACC
Nomura et al., 2012	Delusion subtypes	SPECT	Both hypo- and hyperperfusion in distinct regions in frontal, temporal and parietal areas were correlated with various group factors of delusions
Wu et al., 2020	Depression	MRI (VBM and SBM)	Reduced GM volume in insula was associated with depressive symptoms.

Study	NPS	Imaging technique	Findings
Li et al., 2021	Depression	ASL	Hyperperfusion in right SMG and right supplementary motor area
Levy-Cooperman et al., 2008	Depression	SPECT, MRI	Hypoperfusion in MFG and SFG in depressed AD patients
Honda et al, 2014	Depression	SPECT	Hypoperfusion in inferior frontal lobe associated with depressive symptoms
Liu et al., 2017	Depression	rs-fMRI	Increased ALFF values in the left caudate and thalamus and decreased ALFF values in the left temporal pole in depression
Guo et al., 2018	Depression	rs-fMRI	Increase in functional connectivity between the amygdala and the OFC, reduction in connectivity with medial prefrontal cortex and IFG in depressed participants
Zhang et al., 2017	Depression	rs-fMRI	Asymmetrical alteration in functional connectivity of PCC to right-sided amygdala, parahippocampal gyrus, temporal pole, middle temporal lobe and hippocampus
Guo et al., 2016	Depression	rs-fMRI	Lower degree centrality in the right pre-and post central gyri and in the MFG in depression
Liu et al., 2017	Depression	rs-fMRI	Increased ALFF in the caudate and thalamus, but a decrease in ALFF in the frontal pole, all lateralising to the left in depressed patients
Valotassiou et al., 2021	Eating disorder	SPECT	Eating disorder in AD was associated with hypoperfusion in the left inferior temporal cortex.
Jaramillo-Jimenez et al., 2021	Multiple NPS	MRI	Negative correlation between the amygdala volume and the risk of developing agitation and aggression, positive correlation with the risk of depressive symptoms over the 5-year follow-up.

Study	NPS	Imaging technique	Findings
Torso et al., 2015	NPS	MRI	WML in anterior thalamic radiation were associated with apathy in aMCI
Bruen et al., 2008	NPS	MRI (VBM)	NPS associated with atrophy in: ACC and frontal areas (apathy), right and left IFG, right inferior parietal lobule, left medial frontal gyrus and left claustrum, (delusions), left and right ACC and left insula (agitation)
Boublay et al., 2016	NPS	MRI (VBM), SPECT, PET, CT	Depression, apathy and delusions most consistently mapping to specific brain regions, frontal area of OFC and ACC most involved in multiple NPS
Boublay et al., 2020	NPS	MRI	Reduced volume in SFG, MFG, IFG, ACC and OFC predicted increased NPS over 18 months follow-up.
Balthazar et al., 2014	NPS	rs-fMRI	Positive correlation with Hyperactivity sub-syndrome in the anterior salience network, including the right ACC and the right insula
Munro et al., 2015	NPS	rs-fMRI	Inverse correlation between the Affective sub-syndrome and connectivity in frontoparietal control network. Apathy associated with reduced connectivity within the same network
Serra et al., 2018	NPS	rs-fMRI	Reduced connectivity between VTA and parahippocampal gyrus and cerebellar vermis correlated with irritability, agitation and disinhibition. Disconnection between VTA and striatum as well as insular cortex was linked to increased scores in sleep and eating dysfunction.
Lee et al., 2016	Psychosis	MRI (VBM)	Misidentification: more atrophy in the right hemisphere as compared to psychosis-free participants. Paranoid beliefs: less atrophy in the frontal, temporal and parietal areas when compared with no psychosis

Study	NPS	Imaging technique	Findings
Qian et al., 2019	Psychosis	rs-fMRI	Lower connectivity between left inferior parietal lobule and other regions of DMN
Matsuoka at al., 2018	Sleep disorder	MRI	Reduced GM volume in precuneus
Im et al., 2017	Sleep disorder	SPECT	Decreased perfusion in the bilateral IFG, and temporal pole, right precentral gyrus. Increased perfusion in the right precuneus, right occipital pole and left middle occipital gyrus.

NPS - neuropsychiatric symptoms, MRI - magnetic resonance imaging, VBM - voxel based morphometry, DTI - diffusion tensor imaging, FA - fractional anisotrophy, FDG-PET fluorodextroglucose positron emission tomography, CSF - cerebrospinal fluid, Aβ - amyloid beta, SPECT - single proton emission computed tomography, SBM - surface based morphometry, ASL - arterial spin labelling, SMG - supramarginal gyrus, MFG - middle frontal gyrus, IFG - inferior frontal gyrus, rs-fMRI - resting state functional MRI, VTA - ventral segmental area, ALFF - amplitude of low frequency fluctuations,

1.7.3.8 The potential of neuroimaging in improving prognosis in Alzheimer's disease

As presented above, the research into brain structure and function and their relationship with clinical symptoms of AD has been wide in scope and has yielded a large volume of data that has been contradictory at times. The findings so far have not contributed to knowledge about the determinants of functional decline or the risk of developing neuropsychiatric symptoms in a way that would inform our daily clinical practice. Partially, this may be due to the predominantly cross-sectional design of studies and not making the predictive value of such research its main focus. Yet, the almost universal availability of MRI scanning in clinical populations, which may be further improved by the development of portable and safe imaging technologies such as low-field MRI scanners, provides a unique opportunity to embrace the possibilities that technology and computation now offers for clinical translation. To help address this challenge we designed a study based on a clinical sample of a community-based memory clinic and explored the relationship

between the baseline diagnostic MRI and clinical presentation at 3-year follow up. Better understanding of neuroimaging features that may predict more rapid functional decline and the emergence of non-cognitive symptoms could help us comprehend the disease mechanisms better. It could also help identify those most at risk of a complicated or rapid course of illness and so help us tailor follow-up assessments and interventions for these patients, with practical implications for the way services are structured.

CHAPTER 2. METHODS

2.1 Rationale for the neuroimaging study

Alzheimer's disease is a progressive neurodegenerative condition that may affect patients in different ways, with regards to the rate of cognitive and functional decline as well as the presence and severity of non-cognitive symptoms (Lyketsos et al., 2000, Apostolova and Cummings, 2008, Saari et al., 2018). In a memory clinic, one of the most commonly asked questions - currently impossible to answer precisely - relates to the prognosis. One of the possible ways to improve prediction of individual prognosis is to use neuroimaging techniques, such as MRI which is already employed in clinical assessment of suspected dementia disorders. Neuroimaging has been used extensively to provide an insight into the structure and function of the brain in people with a variety of cognitive disorders, including AD and MCI, but so far has rarely been used in order to predict the sequence of events, the rate of progression or a risk of a particular complication in an individual patient, although researchers have used event-based model constructs to predict the order of events in neurodegenerative diseases including AD (Young et al., 2015).

2.2 Aims of the study

The aim of the research study presented here is to use brain MRI techniques, specifically VBM and rs-fMRI in patients with AD, MCI and SCD in order to identify neuroanatomical regions and changes in functional brain connectivity that may correlate with decline in daily functioning and the burden of neuropsychiatric symptoms at 3-year follow-up, thus providing a tool for more precise prognosis we could give to our patients.

This chapter provides an overview of the tools used for assessing participants in this study, including the basic principles of MRI and of the MRI techniques used for this project (VBM and rs-fMRI), and the rating scales used for assessing ADLs and neuropsychiatric symptoms, the outcome measures of the study and the initial hypotheses as well as the methods.

2.3 The choice of neuroimaging modality

MRI is widely available, safe, non-invasive and acceptable to most patients, including some of those with implantable medical devices, as long as safe scanning conditions are met (Markman et al., 2018). This study uses a clinical cohort of memory clinic patients who have had a structural MRI in the course of their diagnostic process. The participants for this project were recruited from a group of patients who consented to an additional rs-fMRI scan for research purposes. All MRI was conducted at the Clinical Imaging Sciences Centre (CISC), University of Sussex.

Structural MRI has been used in dementia research for a number of years and has produced recognised biomarkers such as hippocampal atrophy (Budinger, 1994, Lorenzi et al., 2015), although a recent review shows that the volume of hippocampus or medial temporal lobe alone has low sensitivity and specificity for predicting the conversion of MCI to AD (Lombardi et al., 2020). However, using quantitative MRI appears to have a more robust value as a biomarker (Gili et al., 2010, Bozzali et al., 2011, Bozzali et al., 2016). Rs-fMRI has been a modality of choice to study functional connectivity in AD as it does not rely on experimental paradigm that often may be challenging for people with cognitive impairment who may have limited capacity to follow instruction (Vemuri et al., 2012). Resting state fMRI studies have been employed extensively in research of normal ageing, MCI and Alzheimer's disease and show widespread disconnection in brain networks that is most evident in AD (Delbeuck et al., 2003, Greicius et al., 2004, Damoiseaux, 2012, Dennis and Thompson, 2014).

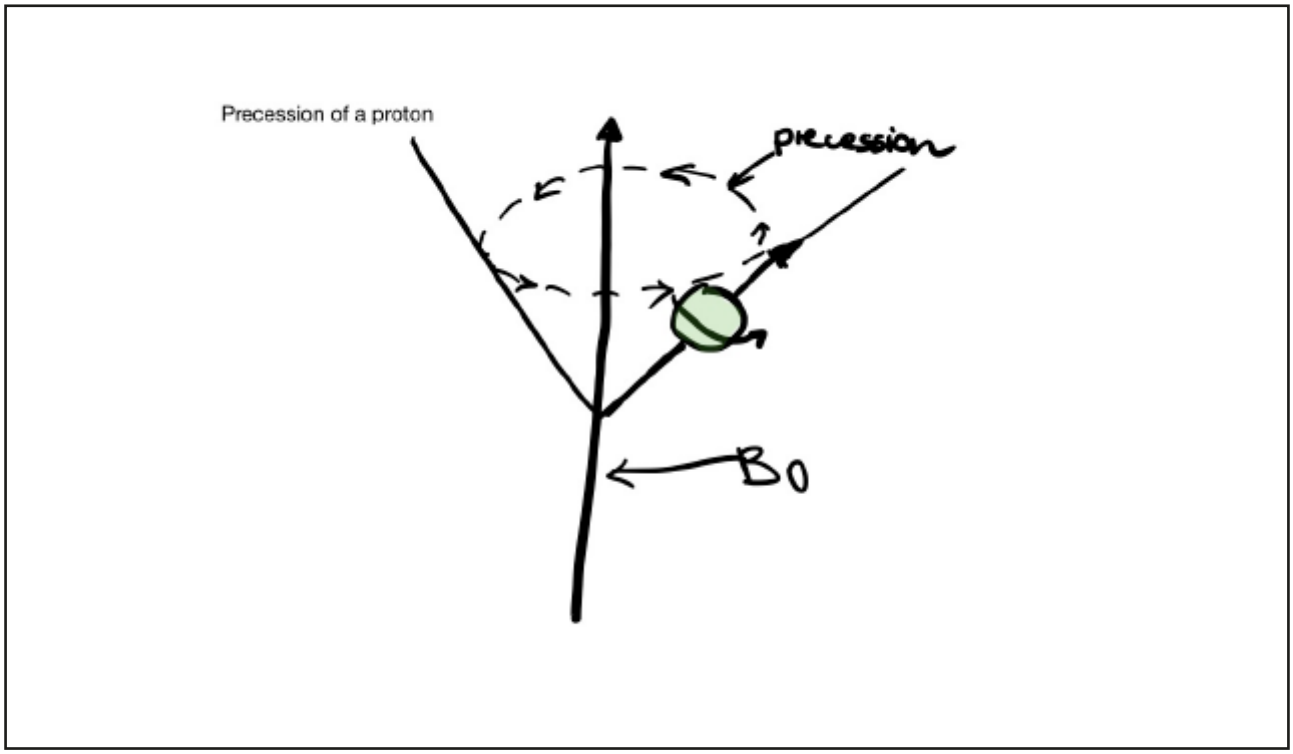
2.3.1 Magnetic resonance imaging principles

MRI is based on the magnetic properties of the protons in hydrogen atoms, present in all tissues of the body containing water molecules. An extensive description of the physics behind MRI is beyond the scope of this thesis, and a simplified overview will be provided here. Detailed explanation can be found in specialised text books (Gadian, 1982). The proton in the hydrogen nucleus is positively charged, and spins around its axis, thus producing a small magnetic field, aligned with the spinning axis, through a movement of an electrical charge. In the absence of an external magnetic field the protons will spin

around in a random direction. Due to this random orientation of the magnetic fields, the sum of their spins, called net magnetisation, is zero (null net magnetisation). When a strong magnetic field - usually expressed with the symbol B0 - e.g. generated by a superconducting magnet in the MRI scanner, is applied to the body, about half of the spins will align in the direction of the field (low-energy state) and the remaining half will align in the opposite direction (high energy state). There is a subtle excess of protons aligning with the direction of the magnetic field (occupying the low energy state), so the net magnetisation will be different than zero and aligned with the static magnetic field B0.

The spinning proton in the presence of a magnetic field B0 gyrates around the axis in a process called precession (Fig. 2).

Figure 2. Precession of a proton (original drawing by MR)



B0 - static magnetic field

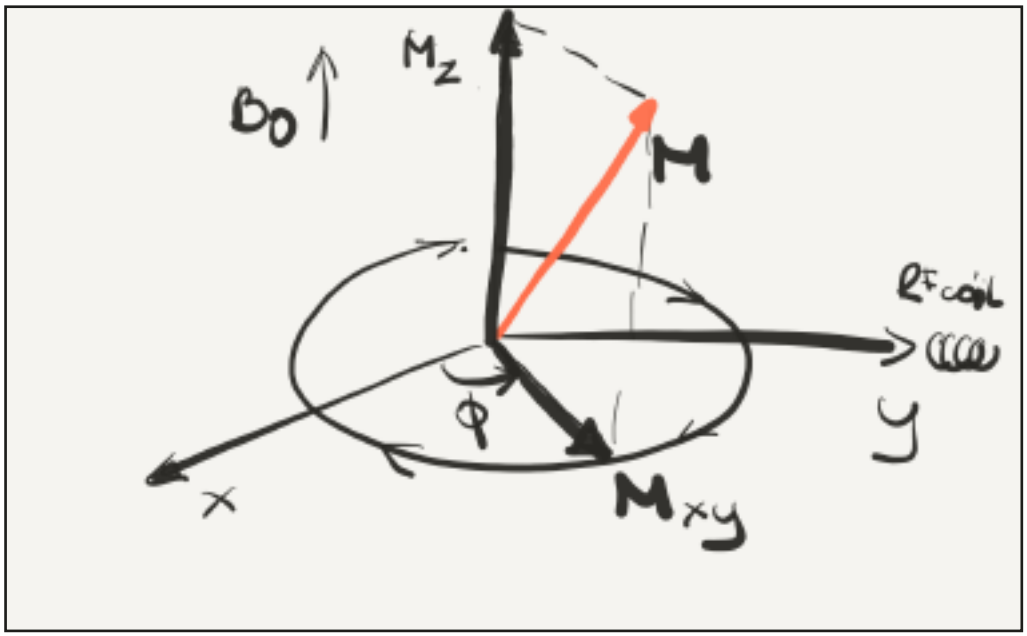
The angular frequency of the precession (ω) is proportional to the strength of the magnetic field through a constant gyromagnetic ratio γ, specific to a particular nucleus, and expressed in the Larmor equation as: $\omega=\gamma B0$ (for hydrogen $\gamma=42.58$ MHz/T).

Resonance is an exchange of energy between two systems happening at a specific

frequency. Magnetic resonance refers to interaction between proton spins and electromagnetic radiofrequency (RF). In MRI scanners, a RF wave is produced in the form of short pulses by the transmit coil. Every RF wave has associated electric and magnetic (B1) fields. Protons that spin with the same frequency as the RF pulse absorb the energy, which leads to their excitation and modification of the spin equilibrium. As stated by the Larmor equation, the strength of the magnet has an impact on the frequency with stronger magnets operating at higher frequency, thus producing more signal.

As explained above, in an MRI scanner, the protons' spins produce net magnetisation in the direction of the main magnetic field B0. The net magnetisation vector (M) can be broken down into longitudinal component Mz, aligned with B0, and transverse component, Mxy, lying in the XY plane (Fig. 3).

Figure 3. Net magnetisation vector (original drawing by MR)



B0 - static magnetic field, M - net magnetisation vector, Mz - longitudinal component of M, Mxy - transverse component of M, RF - radiofrequency wave, θ - tilt angle

At the equilibrium, Mxy=0. When the RF pulse is switched on, the protons start to precess around B1 (magnetic component of the RF) as well as the main field B0 axis, producing a net magnetisation vector tipping down toward the XY plane by an angle (flip angle) depending on the strength and duration of RF pulse (Gadian, 1982).

If a flip angle is 90º, then the magnetisation is fully converted into transverse magnetisation (on xy plane), while the longitudinal component (along z) is zero. Relaxation is the process of returning to the equilibrium, after the RF pulse has been switched off. This occurs through two concomitant but independent processes: the recovery of longitudinal (z) magnetisation, called longitudinal or T1 relaxation, and the decay of transverse magnetisation, i.e. transverse relaxation, or T2.

The time constants of these processes, T1 and T2, differ between soft tissues, and are the basic contrast mechanisms behind clinical MRI. The definition of T1 is the time required for longitudinal magnetisation to recover 63% of its maximum, which differs between various tissues. In the brain, WM has a short T1 time, GM has an intermediate T1 time whilst CSF has a long T1 time. In a T1 weighted image this will correspond to brighter intensity of WM and darker of CSF.

T2 is the time it takes for the transverse magnetisation to decay to 37% of its original value. During the RF pulse protons become ‘in phase’ and when the RF is switched off they start to ‘de-phase’ - a process that depends on a number of effects, including spin-spin interaction, inhomogeneities of magnetic field and tissue-related differences (T2*). The dephasing caused by local inhomogeneities can be recovered using a sequence called ‘spin-echo’. A spin-echo uses an RF pulses of 180º to reverse the phase of spins so that they will come in phase again after an interval equal to that between the excitation pulse and the 180° pulse. When protons are ‘rephased’, they produce an ‘echo’, i.e. a maximum in the observed signal. This strategy is used to produce T2-weighted images (as opposed to T2*-weighted ones, when spin echo is not applied). T2 is related to the water content in tissue. T2 weighted images appear as lighter intensity in the case of CSF and darker in WM, with GM at intermediate intensity.

In the brain T1 is usually longer than T2, though both processes occur simultaneously. The amount of T1 and T2 weighting of an image is controlled through the acquisition parameters. The main ones are the echo time (TE) and the repetition time (TR). TE is the time between the application of 90º RF pulse and the peak signal induced in the coil, which received the MR signal. TR is the time from application of the RF pulse to the next pulse, with TE and TR measured in milliseconds.

2.3.2 Functional magnetic resonance imaging

Functional MRI is based on neurovascular coupling, and on the local changes in magnetic properties of the brain related to increased blood flow to active brain regions. Neuronal activities necessitate an increase in metabolic substrates through an increase in oxygenated blood flow. The differing magnetic properties of oxygenated and deoxygenated haemoglobin (Hb) are the origin of the changes in the MR signal when their proportion changes due to brain activity - oxygenated Hb is diamagnetic, whereas deoxygenated Hb is paramagnetic in relation to the brain and may distort the magnetic field adjacent to capillaries and veins containing deoxygenated blood (Ogawa et al., 1990). During brain activation, oxygen is supplied through the blood in excess of oxygen consumption. This leads to a relative increase on local oxyhaemoglobin, which causes an increase in T2* and a relative increase in MRI signal. This is known as blood-oxygenation-level-dependent (BOLD) contrast (Ogawa et al., 1990, Caballero-Gaudes and Reynolds, 2017)

Most fMRI research has focused on the change in BOLD signal in relation to neuronal activity elicited by a specific task e.g. visualising the activation of the visual cortex during a task where a subject is required to look at images of some sort. Whilst this is an important and useful approach to study a number of cognitive and emotional processes in healthy people and in patient populations, it requires the compliance and consistency of effort of research participants. This can be problematic in a population of people with cognitive impairment and comorbidities, due to potential difficulties they may have with understanding the task, sustaining attention and fatigue. It has been suggested that a better approach in such populations could be studying the function of the brain at rest - without engaging in an externally controlled paradigm (Bozzali et al., 2016). The first observations of intrinsic brain activity at rest and a way in which it appears temporally correlated between distinct brain areas were made over 20 years ago (Biswal et al., 1995). This synchronous activity appears to reflect functional connectivity within a network of brain regions that - although distinct - share the same functional or anatomical connection. (Damoiseaux et al., 2006, van den Heuvel and Hulshoff Pol, 2010). The hypothesis is that brain networks never switch off but rather maintain a “stand-by” status that allows them to become fully functional in a very short time. The synchronous activity detected by BOLD would then be evidence of such stand-by condition. Consistent synchronous activity

between two or more brain regions suggests they may be elements of the same brain network (Eickhoff and Müller, 2015).

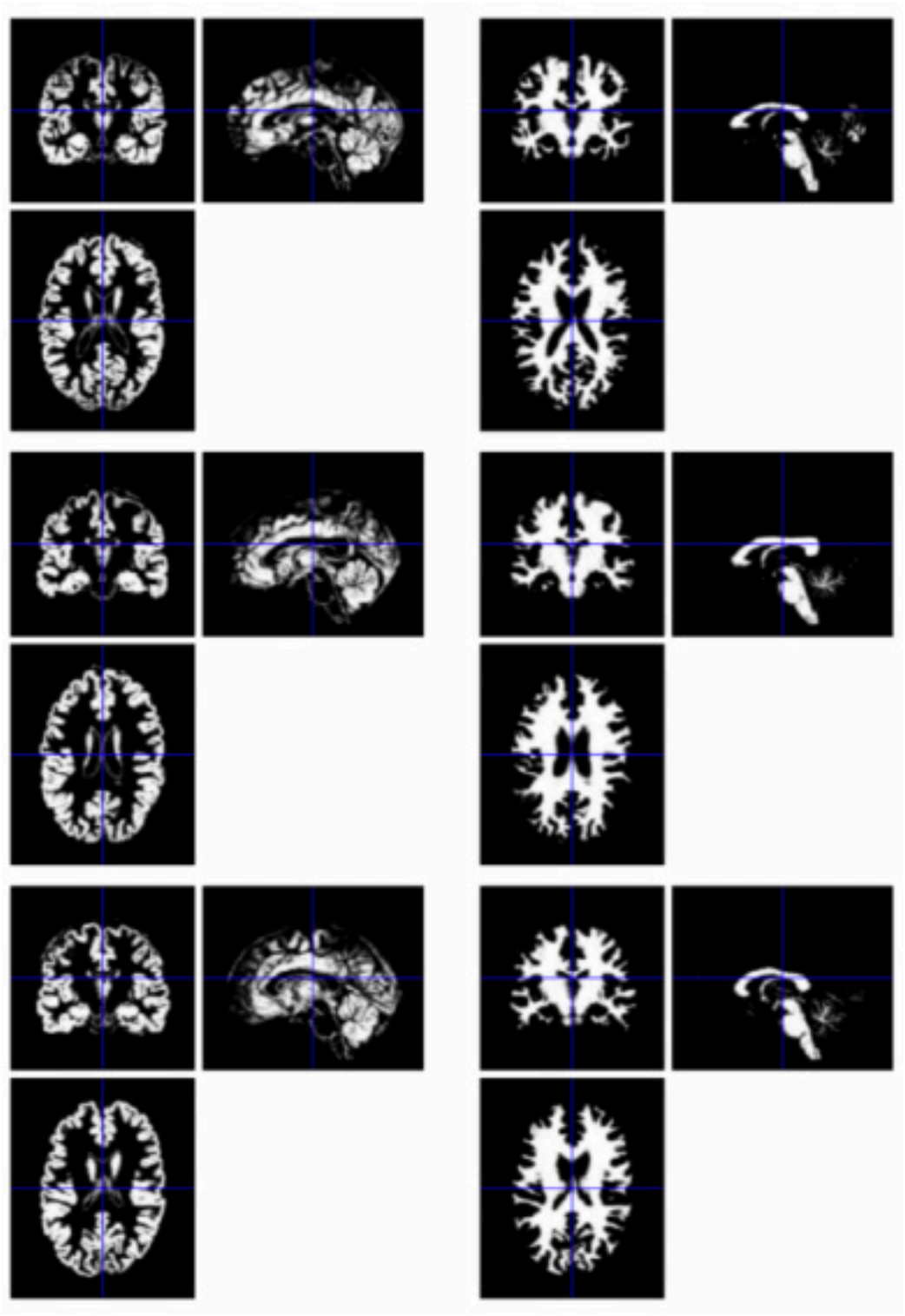
2.4 Quantitative analysis of MRI data

2.4.1 Volumetric analysis

Voxel based morphometry is an unbiased method of analysing the whole brain volume without an a priori regional hypothesis. It involves analysing high-resolution T1 weighted images - such as in our dataset, which comprises of Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE) images (Brant-Zawadzki et al., 1992). The principle of VBM is a voxel-wise comparison of the local tissue volume between groups of people. VBM can also investigate neuroanatomical correlates of subject characteristic, such as specific traits as well as scores e.g. based on performance on tasks. It has been demonstrated before as a useful technique for studying brain correlates of ageing (Good et al., 2001).

VBM preprocessing steps require segmentation of the images (Fig. 4) into GM, WM and CSF, followed by spatial normalisation into the same stereotactic space, and smoothing, similarly to the process described above. Established pipelines are available with software packages such as Statistical Parametric Mapping (SPM - https://www.fil.ion.ucl.ac.uk/spm/). Statistical analysis is performed fitting a general linear model (GLM) at each voxel.

Figure 4. GM, WM and CSF segmentation. Adapted from Ashburner, VBM manual (Ashburner and Friston, 2000).



2.4.2 Resting state connectivity

2.4.2.1 Preprocessing

Preprocessing is an important step in the analysis of fMRI data. This is because the BOLD effect is small compared to the total MR signal, and therefore any sources of noise must be minimised. This is even more important with rs-fMRI, which relies on finding statistical association between spontaneous fluctuations in BOLD signal from spatially segregated brain areas. A typical pipeline would therefore include some motion correction. The simplest approach to this consists of rigid-body registration of each volume in the time series with a reference one. The parameters that map each image onto the reference can then be regressed out of the images. More sophisticated approaches attempt to decompose the signal into BOLD and non-BOLD components, to eliminate the artifactual ones (Salimi-Khorshidi et al., 2014, Pruim et al., 2015).

Other steps of preprocessing include slice timing correction, performed to enable the analytical software to assume all slices were acquired at the same time of the TR, and co-registration with a high resolution image to align functional images with anatomical ones in order to identify the specific regions of brain activation. Each image is then mapped onto a standardised anatomical space (normalisation) so that it can be generalised to a wider population. Smoothing is a form of ‘blurring’ the image to improve signal-to-noise ratio.

Further preprocessing may be needed such as low-pass filtering to remove high-frequency variations, which are unlikely to be linked to the slow-varying haemodynamic response to neural activity. As neural activity is confined to the grey matter, the average white matter and CSF signal can be used as a measure of unwanted signal drift and regressed out.

2.4.2.2 Image analysis

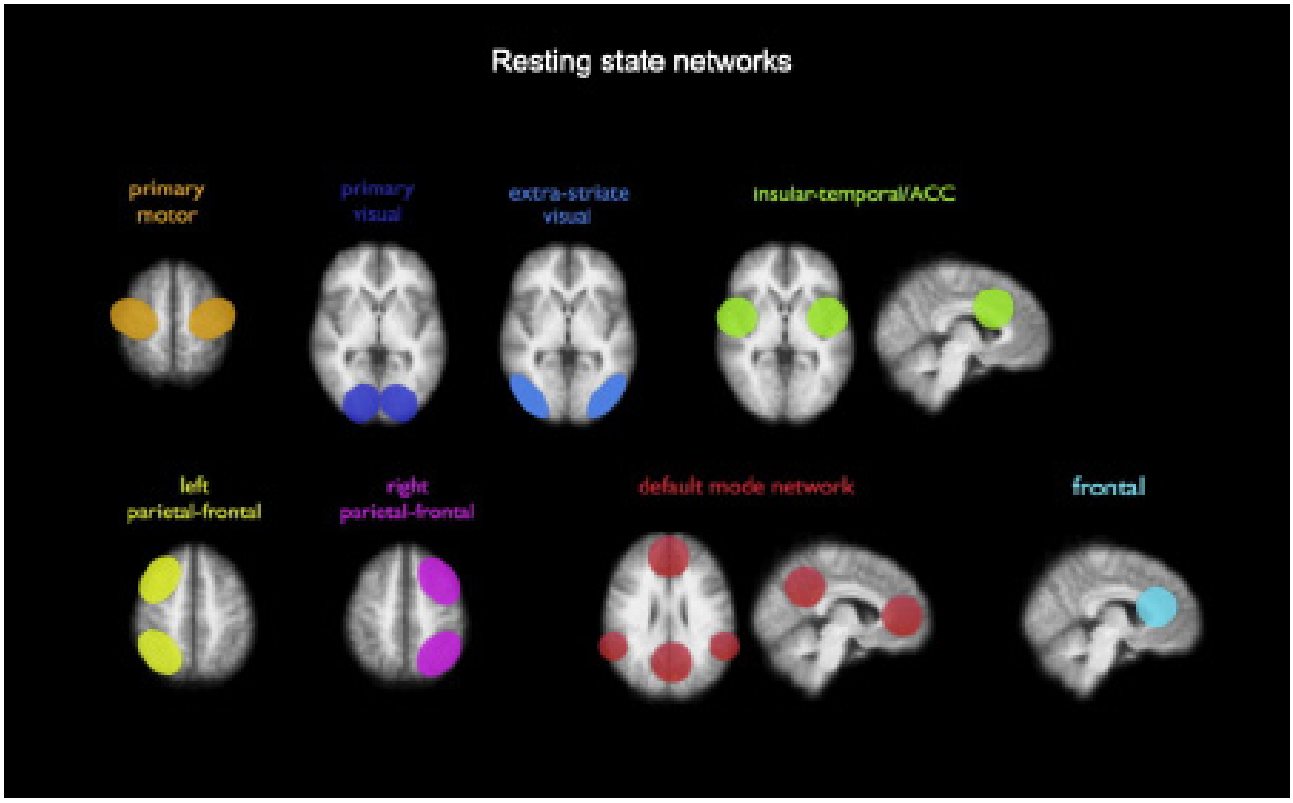
Once cleaned, rs-fMRI data can be analysed in a model-dependent or model-free (or ‘data-driven’) method. Model-free methods are used to look for general patterns of brain connectivity. One such method is Independent Component Analysis (ICA). This approach does not make a priori assumptions and allows for the exploration of whole-brain networks (McKeown et al., 1998, McKeown and Sejnowski, 1998). Spatial ICA used in rs-fMRI analysis is a way of decomposing the multivariate signal into a number of

separate components (some of which will represent resting state networks) through data reduction, by the way of extraction from the BOLD time series of a number of independent components each of which can be interpreted as a network of similar activity (Bozzali et al., 2016). Each component can be described as a spatial map, to reflect the localisation of the detected signal, and a time series to reflect how the signal changes over time (Bijsterbosch J, 2017).

2.4.2.3 Resting state networks

A number of studies have consistently reported the same functionally-linked networks activating during rest, termed resting state networks (Fig. 5) (van den Heuvel and Hulshoff Pol, 2010).

Figure 5. Resting state networks, adapted from (van den Heuvel and Hulshoff Pol, 2010

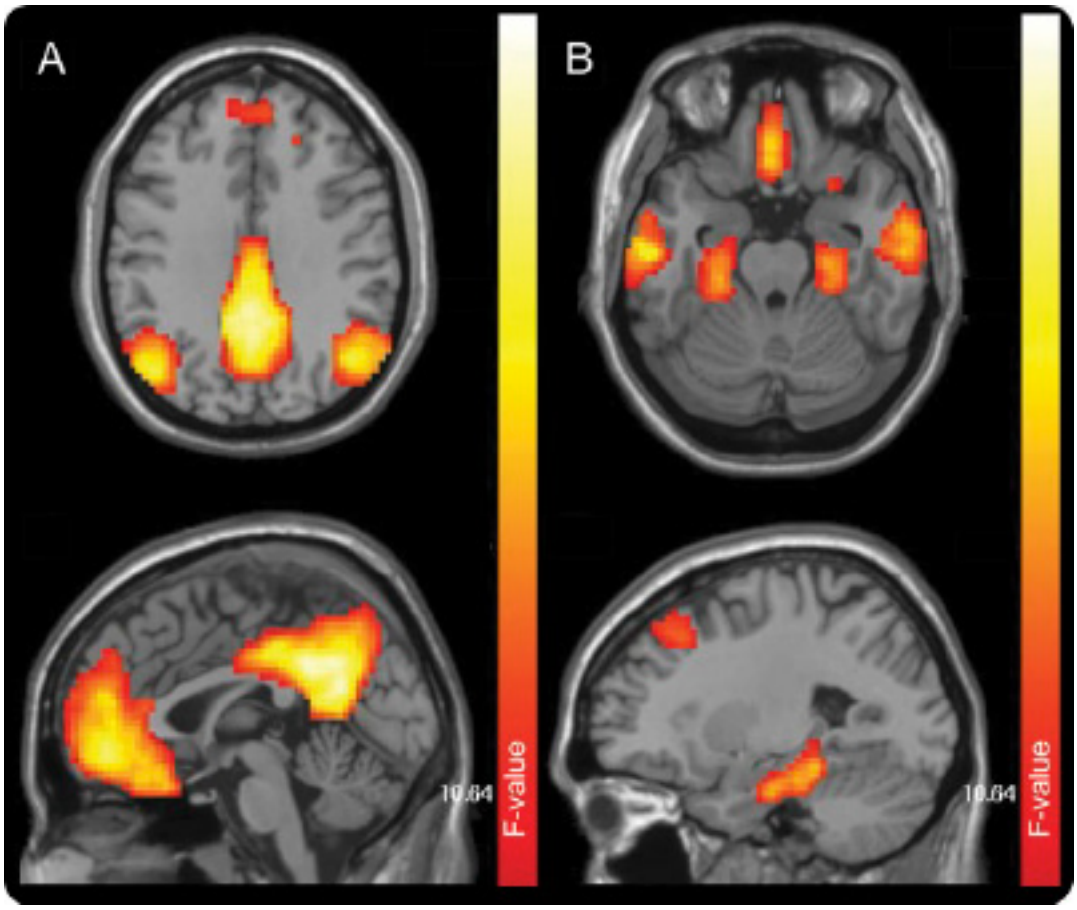


ACC - anterior cingulate

These networks consist of functionally-related, if anatomically separate, brain regions that show high level of synchronous activation during rest.

One of the most studied networks is DMN, which appears to be implicated in a number of cognitive disorders, including Alzheimer's disease (Greicius et al., 2004, Rombouts et al., 2005, Zhou et al., 2015). DMN connects the precuneus and PCC to the medial frontal and inferior parietal region (Fig. 6).

Figure 6. Default Mode Network, adapted from Chhatwal et al., 2013



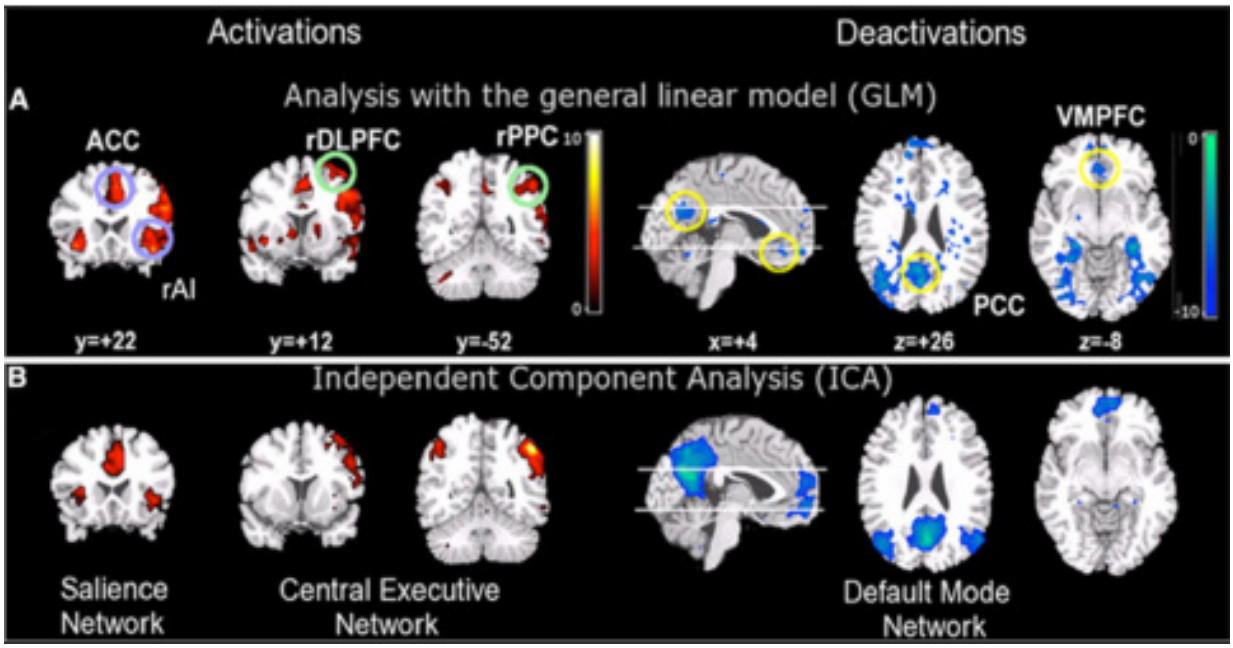
DMN appears to represent a 'default' - baseline brain state and play a role in self-reference, emotional processing, and memory as well as spontaneous cognition and aspects of consciousness (Raichle, 2015, Hohenfeld et al., 2018). Decreased activity in DMN has been a replicated finding in studies involving people with AD and MCI and is postulated as an early marker of increased risk of progression from pre-clinical or milder stage to AD dementia (Wang et al., 2006, Gili et al., 2010, Weiler et al., 2014). Reduced activity in PCC in people with AD is thought to be related to its disrupted connectivity to the hippocampus and entorhinal cortex. The importance of the hippocampus in the function of DMN suggests its involvement in episodic memory processing (Greicius et al., 2004). The most consistent finding appears to be reduction of connectivity within the posterior part of

DMN (precuneus and PCC), although some studies have found an increased connectivity in anterior DMN, which may be a compensatory mechanism to counteract the reduced posterior activity (Vemuri et al., 2012). A longitudinal study found a reduced connectivity in posterior DMN correlated with impairment in episodic memory (Bai et al., 2011).

Other networks of interest in dementia and neuropsychiatric disorders include the salience network, as well as right and left frontoparietal networks. Lateralised frontoparietal networks were found to be activated in cognition-language paradigm, and involved in body perception and pain (Smith et al., 2009). The frontoparietal network is also referred to by some authors as central executive network or cognitive control network (Sridharan et al., 2008, Menon and Uddin, 2010, Menon, 2011, Uddin et al., 2019).

Salience network, incorporating anterior cingulate, orbitofrontal and insular cortex is activated in cognitively demanding tasks and responds to a degree of cognitive, emotional or homeostatic salience (Critchley, 2005, Seeley et al., 2007) (Fig. 7).

Figure 7. Three major brain networks, adapted from Menon and Uddin, 2010 after Sridharan et al., 2008



ACC - anterior cingulate cortex, rAI - right insula, rDLPFC - right dorsolateral prefrontal cortex, rPPC = right posterior precuneus, PCC - posterior cingulate cortex, VMPFC - ventromedial prefrontal cortex

2.5 The choice of rating scales

2.5.1 Activities of daily living

The assessment and measurement of the ability to perform activities of daily living is essential to making the diagnosis of dementia, determining the level of severity and monitoring the progression. There are a number of rating scales used for the assessment of ADL in both research and clinical settings.

BADLS is an informant-completed, validated assessment of functional ability in people with dementia and mild cognitive impairment. It was developed with input from carers of people with dementia, who were consulted about the calibration of meaningful change in the level of daily functioning (Bucks et al., 1996). It is responsive to change and has a good test-retest reliability (Jones et al., 2009). While developed for people with dementia living in the community, its validity, psychometric performance, and practice applicability has been confirmed in a nursing home population with dementia (Boyd et al., 2018).

BADLS consists of 20 domains, covering a wide range of functional abilities incorporating more complex 'instrumental' ADLs as well as the basic ones (e.g. relating to personal care). Additionally, BADLS includes items like mobility and transfers. Mobility and self-care components appear to be influenced by motor function, as demonstrated in a study comparing people with AD and DLB, where the latter cohort had overall more ADL impairment, and there the self-care and mobility scores appear to correlate highly with a Unified Parkinson's Disease Rating Scale (UPDRS) (McKeith et al., 2006). BADLS scores in the original development and evaluation did not differ between men and women and were not susceptible to the effect of education. There was an expected small effect of age (Bucks et al., 1996).

The range of scores from the BADLS is between 0 and 60, with higher scores indicating more severe impairment in ADL. The authors of BADLS have proposed grouping the 20 items into 4 principal components: instrumental ADL, orientation, self-care, and mobility (Table 3).

Table 3. BADLS principal components with item numbers (adapted from Bucks et al., 1996)

Component 1 - IADL	Component 2 - self-care
3. Drink preparation	7. Dental care
15. Use of telephone	6. Hygiene
1. Food preparation	8. Bathing
2. Housework	5. Dressing
3. Communication	9. Using the toilet
4. Shopping	4. Drinking
5. Eating	
Component 3 - orientation	**Component 4 - mobility**
13. Orientation to space	10 Transferring
19. Games and Hobbies	11. Mobility
12. Orientation to time	
20. Driving, using public transport	
18. Managing finances	

IADL - instrumental activities of daily living

2.5.2 Neuropsychiatric symptoms

NPI is a validated scale that rates the severity and frequency of distressing symptoms in 12 domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep and night-time behaviour disorders, and appetite and eating changes (Cummings et al., 1994). It is based on an interview with the person with dementia's carer, a family member or a person who knows the patient well. A screening question is asked first and then followed by more specific sub-questions if the response to the screening one suggest an abnormality might be present. The carer is asked to rate the frequency of the symptoms on a scale from 1 to 4 (1 - rarely, less than once per week, 2 - sometimes, about once per week, 3 - often - several times per week but less than daily, and 4 - very often - once or more per day). The carer is then asked to rate the severity of a given symptom, on a scale of 1 to 3 (1 - mild, 2 - moderate and 3 - severe). Each level of severity is described

further per domain. A composite score is obtained by multiplication of frequency and severity. The carer is also asked to rate the level of their distress any present symptom causes on a scale of 0 (not at all) to 5 (very severely).

NPI has good psychometric properties including content validity, concurrent validity, and reliability (Table 4). It does not appear to be influenced by normal ageing (Cummings, 1997).

NPI has been developed to assess psychopathology in dementia, but it has been used in MCI in longitudinal studies and in clinical trials setting (Teng et al., 2007, Cummings et al., 2013, Cummings et al., 2014).

Table 4. Features of Neuropsychiatric Inventory (adapted from Cummings, 1997)

Caregiver based, does not require patient's cooperation and can be used in very disturbed or advanced disease patients
Screening question strategy minimises administration time
Assesses both frequency and severity of neuropsychiatric symptoms
Assesses caregiver distress associated with individual neuropsychiatric abnormalities
Provides a profile of behavioural changes that helps to distinguish AD from other types of dementia
Assesses conventional types of psychopathology that are readily recognised by clinicians and commonly require treatment
Well-established psychometric properties
Sensitive to drug-induced behavioural change
Comprehensive
Available in many languages
Instructional module describing administration and scoring techniques
Video available demonstrating its application

2.5.3 Cognitive functioning

The Addenbrooke's Cognitive Examination - revised (ACE-R) is a widely used cognitive battery, which has been developed to provide a brief yet sensitive and specific screening instrument (Mioshi et al., 2006). It was developed from the Addenbrooke's Cognitive Examination (ACE) to improve sensitivity and cross-cultural usage. The items of the test combine to a total score of 100 points and are divided into five cognitive domains: attention and orientation (18 points), memory (26 points), verbal fluency (14 points), language (26 points) and visuospatial skills (16 points). The ACE-R has a better sensitivity to detect dementia than the Mini Mental State Examination (MMSE), although it incorporates its items (Folstein et al., 1975). Its sensitivity to dementia is high and ranges between 84-94% dependent on the cut-off score (Mioshi et al., 2006), with superior diagnostic accuracy compared to the MMSE (Crawford et al., 2012). It is well validated and is recommended in use in primary care, hospital setting and specialist memory clinics. (Velayudhan et al., 2014).

2.6 Outcome measures

2.6.1 Neuroimaging

The primary outcome measures in this study are quantitative data parameters from participants' scans for VBM and rs-fMRI

- rs-fMRI to measure functional connectivity by means of synchronicity in temporal BOLD fluctuations and identify resting state networks

- VBM - regional GM volume

These parameters will be used to study the following respectively:

a) The ability of functional connectivity assessed by rs-fMRI at baseline to predict change in ADL, and the presence of neuropsychiatric symptoms 30 months later.

b) The correlation of baseline regional brain volume with rate of functional decline and neuropsychiatric symptoms at 3-year follow-up.

2.6.2 Clinical measures

Clinical measures of functional decline and neuropsychiatric symptoms include:

- Bristol Activities of Daily Living Scale (BADLS) (Bucks et al., 1996);
- Neuropsychiatric Inventory (NPI) (Cummings et al., 1994);
- Change in clinical diagnosis between baseline and follow-up assessment;
- Assignment of fast vs slow decliner category (BADLS follow-up - BADLS baseline =/> 15; BADLS follow-up - BADLS baseline between 0-8); and
- Assignment of high (10+) vs low (0-9) burden of neuropsychiatric symptoms.

2.7 Research questions

This project aims to address the following questions:

1. Is there a correlation between regional brain volume at baseline and change in ADL?
2. Is there a correlation between brain connectivity at baseline and the change in ADL?
3. Is there a correlation between regional brain volume and neuropsychiatric symptoms?
4. Is there a correlation between brain connectivity and neuropsychiatric symptoms?

2.8 Hypotheses

1. It is hypothesised that there will be a negative correlation between brain volume and performance in ADL.
2. It is hypothesised that there will be an inverse correlation between ADL performance and functional connectivity.

3. It is hypothesised that there will be a negative correlation between regional brain volume at baseline and presence of neuropsychiatric symptoms at 3-year-follow-up.

4. It is hypothesised that a disruption of specific brain networks at baseline will correlate with neuropsychiatric symptom scores in specific symptoms and sub-syndromes.

2.9 Original contribution to science

The literature review as outlined above shows a growing body of research exploring the neural correlates of aspects of AD and MCI. What has been missing so far is how knowledge of structural and functional changes in the brain of people with AD across the spectrum of severity can inform prognosis, specifically with regards to changes in ADL and the risk of neuropsychiatric symptoms. Recently, large international studies have been designed using multi-centre databases of imaging and clinical data (e.g. ADNI). However, despite efforts to include large numbers of participants these populations are still relatively selective by the virtue of coming from highly specialised, tertiary referral centres and so their cohorts are not always representative of 'real-life' local populations. The development of imaging automatic classification methods based on samples of local population would be a valuable tool to aid diagnosis through the use of MRI, a routinely available, acceptable and low-cost technique. The focus on non-cognitive symptoms that may present very early in the course of AD, even before significant cognitive difficulties, offers an opportunity to study the unique nature of problems like depression or apathy in AD patients.

This study tests the predictive utility of brain MRI, an easily accessible and cost-effective imaging technique to help with future planning of person-centred and personalised care in dementia.

2.10 Participants

Participants for this research were identified from patients who attended an assessment due to cognitive complaints in the West Sussex Memory Assessment Service (MAS) between 2012 and 2015.

2.10.1 Inclusion and exclusion criteria

The MRI data were collected as part of the project 'A study of brain structure and connectivity in patients referred to community memory clinics'. This included 180 male and female memory clinic patients, from whom potential participants for this PhD study were identified by meeting the following criteria:

2.10.1.1 Inclusion criteria

- Received a diagnosis of Alzheimer's disease according to National Institute of Ageing and Alzheimer's Association (NIAAA) criteria (McKhann et al., 2011), or amnestic mild cognitive impairment (Petersen, 2004) or expressed subjective cognitive concerns.
- Had a baseline clinical assessment in the course of dementia diagnostic pathway, including quantitative assessment of cognition and ADL.
- Had a structural and rs-fMRI scan at CISC.
- Between 50-95 years old.
- Speaking fluent English.
- Able to provide informed consent, or in case of lack of capacity to provide informed consent they had a relative or a carer able to act as a personal consultee.

2.10.1.2 Exclusion criteria

- A history of significant excessive alcohol use (history of alcohol dependence, clinical features suggestive of alcohol related cognitive impairment).

- Presence of significant intracranial pathology [multiple infarcts, severe cerebral amyloid angiopathy (CAA), severe small vessel disease - graded as stage 3 in Fazekas scale (Wahlund et al., 2001)].

2.10.2 Ethics

2.10.2.1 Ethical approvals

The project in which the imaging data were collected 'A study of brain structure and connectivity in patients referred to community memory clinics' was approved by South East Coast and Surrey Research Ethics Committee on 19.12.2012 (approval number 12/LO/1438). The approval for the research presented here 'Brain structure and connectivity as predictors of functional decline and neuropsychiatric symptoms in Alzheimer's disease' was provided by the London Queen Square Research Ethics Committee on 21.04.2016 (approval number 16/LO/0633, Appendix 1).

2.10.2.2 Recruitment

All recruitment and study procedures, including identifying and contacting potential participants, capacity assessment, informed consent process, and completion of clinical measures were carried out by the doctoral researcher (MR). A number of patients who were originally eligible to participate were lost to follow-up at the time of recruitment. Some were excluded due to a change in diagnosis so not meeting the eligibility criteria (e.g. some potential participants were diagnosed with other brain conditions in the interval between their original diagnosis and being invited into the study).

An invitation to participate in the study was sent by letter to all those eligible, followed up by a phone call. The letter and the phone call were addressed to the patient, unless the medical records listed another person as the 'preferred contact', in which case that identified person received the letter and the subsequent phone call. This procedure was recommended by the members of Dementia Consultation Group - a local Patient and Public Involvement (PPI) group, following their review of the study proposal. Patients and their carers who expressed interest in participation were sent a Participant Information Sheet (PIS, Appendices 1-2), as well as a Carer Information Sheet (Appendix 4) and a Personal Consultee Information Sheet (Appendix 5). The latter was included in case the

potential participant lacked capacity to consent to taking part in this research.

2.10.2.3 Capacity and consent

A capacity assessment was completed with all participants before the consenting procedure at the study visit. All participants with dementia had a choice of identifying a personal consultee - usually the carer who provided informant-based input and who acted on behalf of the participant for the purpose of the study. The potential participants had at least 48 hours to consider the information included in the above documents.

Participants who expressed a wish to take part in the study after reading the PIS were seen and assessed during one study visit (with the exception of one participant who was seen on two occasions as she could not tolerate the length of the assessment). All participants were given a choice of a home visit (preferred by most) or a clinic-based assessment. At the beginning of the study visit a capacity assessment was carried out in accordance with the principles covered by the Mental Capacity Act 2005. Participants who were deemed to have capacity signed the informed consent form (Appendix 6). Participants who lacked capacity to give a fully informed consent but were happy to participate identified a personal consultee, who signed the Personal Consultee Declaration Form (Appendix 7).

2.10.3 Clinical Assessment

The study visit included the following:

a. Application of the diagnostic criteria for AD (McKhann et al., 2011) or MCI (Petersen, 2004) to establish the validity and stability of the diagnosis;

b. Cognitive assessment - Addenbrooke's Cognitive Examination - revised (ACE-R) (Mioshi et al., 2006);

c. ADL assessment - Bristol Activities of Daily Living Scale (BADLS) (Bucks et al., 1996);

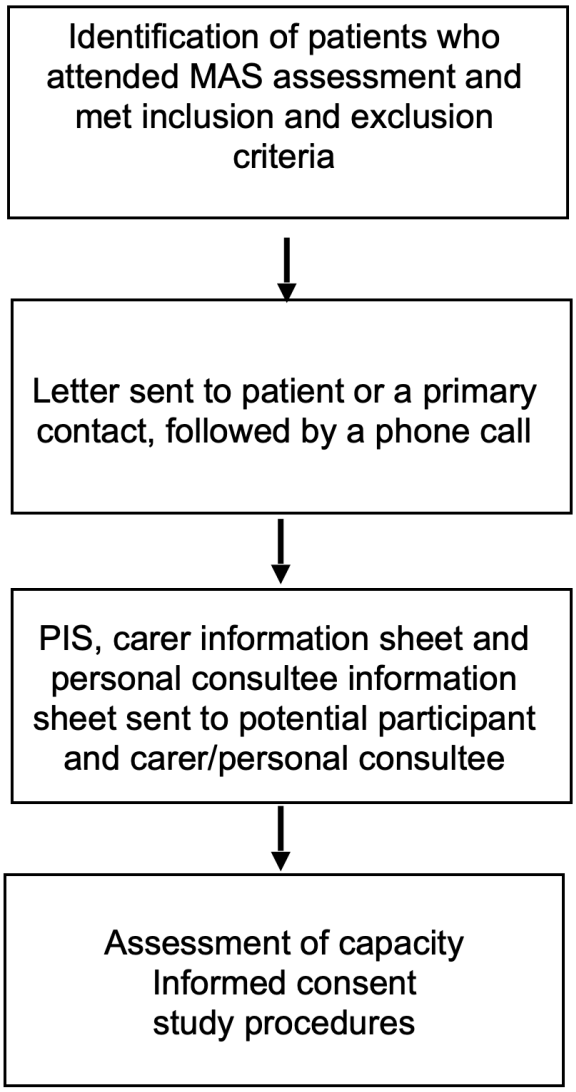
d. Assessment of neuropsychiatric symptoms - NPI (Cummings et al., 1994);

e. Clinical interview reviewing and updating information collected and recorded in clinical records at baseline, including place of residence and care provision, age when leaving full-time education, and presence of vascular risk factors and co-morbidities. The latter included hypertension, type 2 diabetes, hypercholesterolaemia, ischaemic heart disease, and atrial fibrillation.

Additionally, the neuroradiologist clinical report on the baseline MRI scan was reviewed and coded as described further in section 2.12.

The visit took between 60 and 90 minutes. Figure 8 illustrates the recruitment and study procedures process.

Figure 8. Study procedures



MAS - memory assessment service, PIS - participant information sheet

2.10.4 Dichotomised diagnostic classification

For the purpose of our analyses, we dichotomised participants into two groups, based on their diagnostic category at the time of the follow -up visit:

- Participants who met the NIA-AAA core clinical criteria for the diagnosis of probable AD dementia (McKhann et al., 2011) are further referred to as 'AD' group .

- Participants who presented with aMCI or subjective cognitive complaints, i.e. did not meet the above criteria for AD dementia are further referred to as 'non-AD' group.

The diagnostic classification was not based on biomarker confirmation.

2.11 MRI acquisition

All participants had a volumetric structural MRI and resting state functional MRI. The structural images were used together with all clinical initial assessment data to establish a diagnosis. All imaging was obtained, in a single session, using a 1.5T MRI scanner (Siemens Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) at CISC, between 2012 and 2015. The MRI acquisition protocol included:

a. A T2-weighted turbo spin echo (TSE) (repetition time (TR)=3820 ms, echo times (TE)=93 ms, echo train length (ETL)=16; matrix=512×330; field-of-view (FOV)=230×192 mm^2; 22x5 mm thick slices, with an inter-slice gap of 1.5mm);

b. A fast fluid attenuated inversion recovery (FLAIR) (TR=9720 ms, TE=89 ms, inversion time (TI)=2578 ms; ETL=16; matrix=256x224; FOV=230x201 mm^2, 22x5 mm thick slices, with an inter-slice gap of 1.5 mm);

c. A T2*-weighted gradient-echo (TR=999 ms; TE=25ms; flip angle=20°; matrix=256x192; FOV=240x240 mm^2; 22x5 mm thick slices, with an inter-slice gap of 1.5 mm);

d. Diffusion-weighted echo-planar imaging (EPI) with maximum b-value of 1000 s/mm-2 and diffusion gradients along 3 orthogonal directions (TR=6200ms; TE=156 ms;

matrix=192x192; FOV=230x230 mm^2);

e. 3D Magnetisation prepared rapid acquisition gradient echo (MPRAGE) (TR=1160 ms, TE=4.24 ms, inversion time = 600 ms; flip angle= 15 °; Matrix=256x256, FOV=230x230 number of slices=192, thickness=0.9 mm);

f. A T2*-weighted EPI sensitised to BOLD contrast (TR=2300 ms, TE=45 ms, 30 axial slices parallel to AC-PC line, matrix=64×64, pixel size=3×3 mm^2, slice thickness=4 mm, inter-slice gap = 0.4 mm; flip angle=90°) for resting-state fMRI (total number of volumes=300). During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep.

For the purpose of this doctoral thesis, only MPRAGE and T2* weighted EPI images were used in quantitative analysis.

2.12 Image analysis

All MRI images were reviewed for the clinical purpose of aiding the diagnostic process by a consultant neuroradiologist with special interest in cognitive disorders. The consultant had worked in the field of neuroradiology for over 20 years and completed a PhD on the application of VBM in health and neurological disease, including dementia. She is the lead for Dementia Imaging and for Neuroscience Imaging Research in her dual role as a Consultant Neuroradiologist at University Hospitals Sussex NHS Foundation Trust and as an Honorary Senior Lecturer with Brighton and Sussex Medical School. She co-authored Radiology Reporting Templates for Dementia in 2019.

The descriptive reports included information about hippocampal atrophy, presence of microvascular and large vessel disease, as well as presence and number of microhaemorrhages. The neuroradiologist used the following semi-quantitative scales to further describe the visually rated pathologies:

- Medial Temporal lobe Atrophy (MTA) scale to rate the cortical atrophy of the hippocampus (Scheltens et al., 1992) and

- Fazekas scale to rate the severity of microvascular disease (Fazekas et al., 1987, Wahlund et al., 2001).

MTA scale is based on visual rating of brain structures performed on T1 weighted coronal sections through the hippocampus at the level of anterior pons (Scheltens et al., 1992). It considers the width of the choroid fissure and the temporal horn of the lateral ventricle, as well as the height of the hippocampus. The score ranges from 0 to 4, with the following description:

0 - no CSF around the hippocampus,

1 - slight widening of choroid fissure,

2 - moderate widening of choroid fissure as well as mildly widened temporal horn of the lateral ventricle and mildly reduced height of the hippocampus,

3 - marked widening of choroid fissure, moderately widened temporal horn and moderate reduction of hippocampal height,

4 - marked widening of choroid fissure, marked enlargement of the temporal horn and marked atrophy and loss of internal structure of the hippocampus (Scheltens et al., 1992).

The interpretation of the MTA score in the context of pathological change is age-dependent, as validated in a memory clinic sample by Claus and colleagues (Claus et al., 2017). We used the age-dependent classification to rate the hippocampal atrophy as present as follows:

- under 65 years - MTA ≥ 1
- 65-74 years - MTA ≥ 1.5
- 75 years and over - MTA ≥ 2.

The Fazekas scale is used as a visual rating of the extent of white matter hyperintensities, broadly reflecting small vessel disease, performed on the T2 weighted MR images

(Fazekas et al., 1987). The scale considers WM changes in periventricular and deep white matter, each of these regions is given a score between 0 and 3 dependent on the number, size and ‘confluence’ of hyperintensities.

Fazekas at al graded periventricular hyperintensities as follows:

0 - absent,

1 - ‘caps’ or pencil-thin lining,

2 - smooth ‘halo’,

3 - irregular periventricular hyperintensities extending into the deep white matter.

Deep white matter hyperintensities, which are more closely linked to small vessel pathology (Kim et al., 2008), were classified as follows:

0 - absent,

1 - punctate foci,

2 - beginning confluence of foci

3 - large confluent areas (Fazekas et al., 1987).

The descriptive reports were reviewed and coded to reflect the presence and severity of the pathologies listed above in the following manner:

a. hippocampal atrophy - present or absent

b. small vessel disease - absent, mild, moderately severe

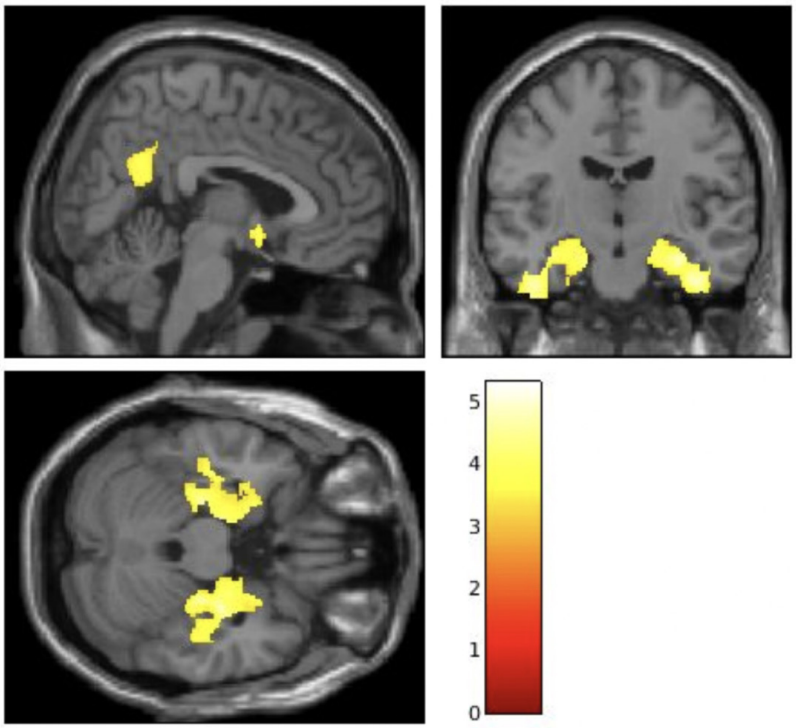
c. microhaemorrhages - absent, solitary, multiple.

To avoid the confounding effect of cerebrovascular disease we excluded patients with severe small vessel disease (Fazekas score > 2), multiple micro haemorrhages (n>10), and focal infarcts.

2.12.1 Voxel based morphometry

T1 MPRAGE images are analysed according to the VBM pipeline in Statistical Parametric Mapping, 12th edition (SPM12) package. We have used computational anatomy toolbox for SPM12 (CAT12) for segmentation of the brain into GM, WM and CSF. VBM (Ashburner and Friston, 2000) covered under the CAT12 package, is a procedure that was developed to enable the analysis of regional GM volume on voxel-by-voxel basis. The algorithm implemented in SPM12 uses an integrated approach (Ashburner and Friston, 2005) that includes bias correction, image registration to the Montreal Neurological Institute (MNI) template and tissue classification (segmentation) into GM, WM and CSF. The segmentation iteratively brings images from different participants into alignment (normalisation). This is achieved using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007). As the output of VBM are probabilistic maps of each tissue (i.e. images with values ranging from 0 to 1, where 0 indicates absence of that specific tissue, and 1 indicates that the whole voxel is filled with – say – GM), an additional step, known as “modulation” is included. Modulation consists of scaling with the Jacobian determinants, which measure how the voxel volume changes after registration, derived in the registration step. This step allows for the volume of tissue from each structure to be preserved after warping. The resulting modulated images were smoothed with an 8 mm full width at half-maximum isotropic Gaussian kernel. This yields GM and WM maps in standard space, which can be correlated with the clinical variables.

Figure 9. VBM image showing between-group regional differences in brain volume between patients with stable MCI and this who converted to dementia (image from a separate analysis on the study dataset, MR)



2.12.2 Resting state functional MRI

Rs-fMRI data were processed using tools from the FMRIB Software Library (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). Preprocessing was performed using fMRI Expert Analysis Tool (FEAT) - a software tool that can be used with a graphical user interface (GUI). The steps performed on each dataset are summarised below.

After removing the first 4 volumes to compensate for T1 saturation effects, rs-fMRI data were first pre-processed to remove the effects of involuntary motion. In FEAT this is done using MCFLIRT - an intra-modal fully automated motion correction tool (Jenkinson et al., 2002) that uses rigid-body registration to realign the fMRI time-series using the middle volume as the reference. The motion parameter were reviewed to exclude participants with average absolute and time-wise displacement > 1 mm (Power et al., 2012). Non-brain tissue is then removed using the Brain Extraction Tool from the FMRIB software library (FSL).

Each participant's dataset was co-registered to their MPRAGE scan, following which a non-linear normalisation to the MNI space was performed. We then regressed out from the fMRI data the average WM signal, the average CSF signal and the realignment parameters estimated by MCFLIRT at an earlier stage. Data were re-sliced to 2x2x2 mm^3 and spatially smoothed by filtering them with an 8 mm Gaussian kernel. Finally high-pass (> 0.01 Hz) temporal filtering was applied to remove very slow variations.

We used the MELODIC (Multivariate Exploratory Linear Optimised Decomposition into Independent Components) tool employing group ICA (GICA) to decompose our spatial and temporal fMRI dataset into 30 different spatial maps (components). A group ICA identifies the functional networks of interest at group level, and a dual-regression is then applied to identify the corresponding components at individual level. The resulting maps can be used for group comparison, and for investigating the correlation with behavioural and clinical measures.

Once the 30 spatial maps were identified, all were reviewed and checked against the published research to identify the components representing 'real' resting state networks. Keeping in mind the relevance of network disruption in cognitive and psychiatric disorders we have chosen the following network for further analysis: default mode network (DMN), left and right frontoparietal network (FPN), and salience network (Zhong et al., 2014) (Neufang et al., 2011, Agosta et al., 2012).

The voxelwise correlation between subject-specific functional connectivity maps of the relevant resting-state networks and behavioural variables was assessed by permutation tests, using cluster-based inference within the FSL tool randomise (Winkler et al., 2014) that employed 5000 permutations per test and contrast. Both positive and negative associations were tested, and analyses were adjusted for age and gender. Correction for multiple comparisons was performed according to the threshold-free cluster enhancement (TFCE) option (Smith and Nichols, 2009) and p-values were considered significant if lower than 0.05 Individual functional maps have been correlated with changes in BADLS and NPI scores.

2.13 Clinical assessment and rating scales

2.13.1 Activities of daily living assessment - BADLS

The BADLS scale has been chosen to use for the assessment of activities of daily living in the study population. The ADL change was calculated by taking the difference between the BADLS measured at baseline and at follow-up. These data were analysed in two ways, first as a continuous variable (BADLS change score) and second as a dichotomised variable with participants divided into two groups:

- stable or little decline (<9 points)

- significant decline (15+ points)

The choice of dichotomising the change in BALDS score as clinically meaningful was made on the basis of previous studies using BADLS as an outcome measure in intervention trials (Courtney et al., 2004) and the distribution of scores in this cohort. A 3.5 points change in BADLS score over 52 weeks has been identified as a 'minimum clinically important' difference (Howard et al., 2011).

The correlation analyses of GM volume and brain connectivity included:

- total baseline and total follow-up BADLS score

- change in total BADLS score (BADLS follow-up - BADLS baseline)

- principal components analysis (analysis of baseline and follow-up BADLS items in Instrumental, Orientation, Self-care and Mobility factors)

2.13.2 Neuropsychiatric symptoms assessment - NPI

Neuropsychiatric assessment was completed 30 months (+/- 6 months) after the initial assessment and diagnosis with the NPI (Cummings et al., 1994). Presence of non-cognitive symptoms - based on the NPI score at follow-up assessment, was analysed

in two ways, first as a continuous variable (NPI score at follow-up) and second as a dichotomised variable with participants divided into two groups:

- no or mild non-cognitive symptoms (NPI score of 0-9)

- significant non-cognitive symptoms. NPI score of 10+)

2.14 Statistical analysis of clinical data

The IBM Statistical Package for Social Sciences (SPSS) version 27 was used to analyse parametric and non-parametric clinical data. Descriptive statistics were used to calculate means, medians, range and standard deviation. Parametric tests such as independent sample t-tests were used to compare means for continuous variables between groups. Non-parametric tests, such as Mann-Whitney U tests were used to compare non-normally-distributed continuous data between groups. Pearson Chi-Square tests were used to compare categorical and nominal variables between groups.

2.15 Post-hoc power estimates based on sample size

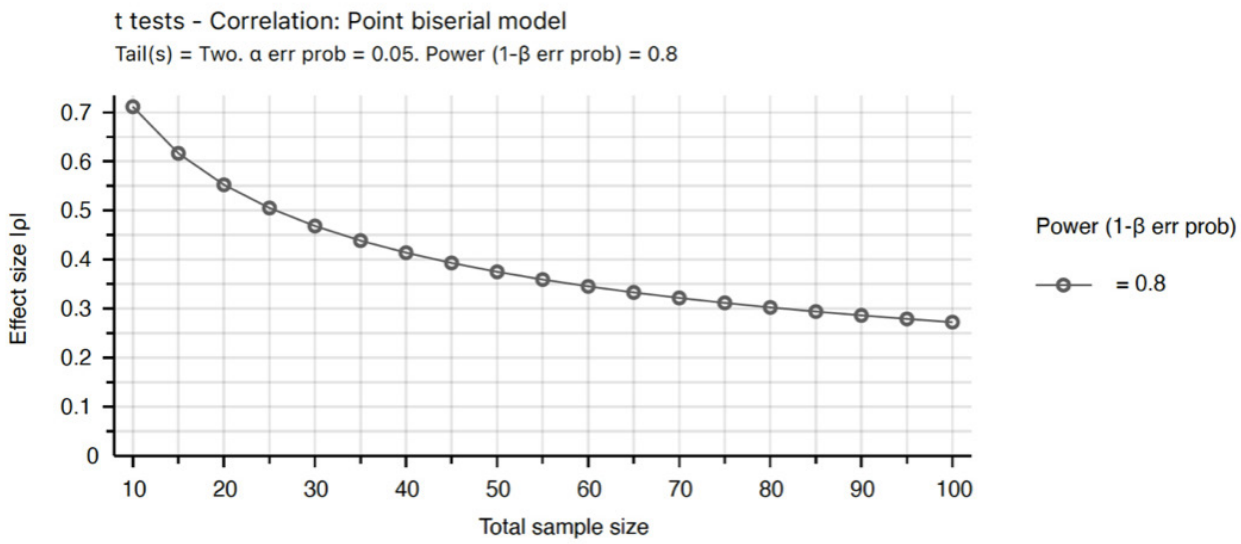
This study was based on data collected from patients referred for a clinical scan, who agreed for their imaging data to be used for research. The numbers were fixed by the earlier imaging data and therefore we did not carry out pre-study power calculations. Seventy-nine of those participants were recruited to the study to obtain the follow-up clinical measures, of whom 65 had fMRI data of sufficient data quality.

In order to evaluate the power of the study, we conducted a post-hoc sensitivity analysis to determine the effect size required to detect an effect with correlation analysis in a sample of 65 individuals. Although standard statistical methods do not fully translate to imaging analysis, we performed this sensitivity analysis using G*power 3.1 (Faul et al., 2007), assuming 80% power. The required effect size for a two-tailed significance $\alpha=0.05$ is 0.33, which is considered medium (Cohen, 2013)

We also plotted the effect size (ρ) as a function of the sample size (Fig. 10), which shows that the effect size decreases relatively slowly with the number of participants, and

therefore a much larger sample size (over 100 participants) would have been required for detecting small effects (around 0.1). The graph shows that for a sample size of 79, we can detect an effect of 0.3, whilst for a sample size of 65 (in connectivity analysis) we can detect an effect size of 0.33. The plot was obtained using G*power 3.1 (Faul et al, 2007).

Figure 10. Required effect size as a function of the sample size for 80% power and a two-tailed significance α=0.05



α - type-1 error, β - type-2 error, ρ -effect size

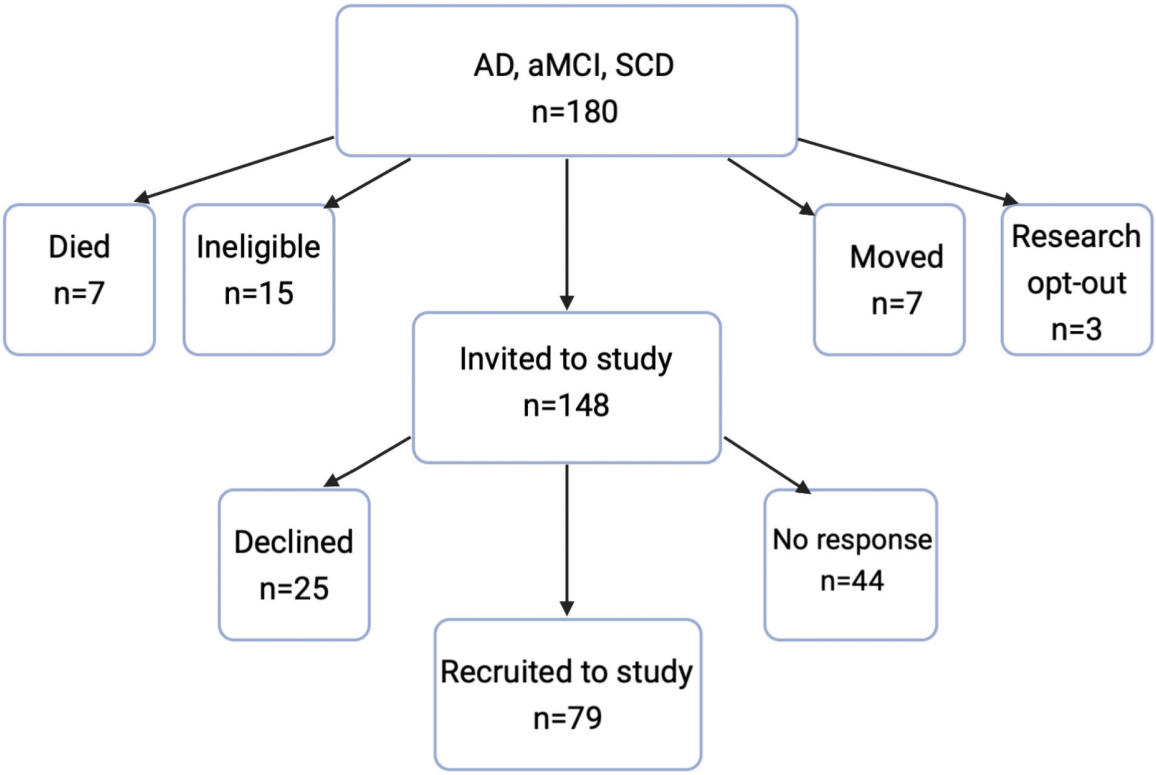
CHAPTER 3. Results

3.1 Clinical sample data

In this chapter the characteristics of the participant sample and the results of analysis of clinical variables is presented.

3.1.1 General description of the cohort

Figure 11. Recruitment flowchart



AD - Alzheimer's disease, aMCI - amnestic mild cognitive impairment, SCD - subjective cognitive decline

One-hundred-and-eighty patients of the West Sussex memory clinic, who participated in a project 'A study of brain structure and connectivity in patients referred to community memory clinics', during which they underwent structural and rs-fMRI, were identified as potentially eligible to be approached about participation in this PhD research. These patients all consented at the time of their MRI scan to being approached in the future about

other studies and fulfilled criteria for the diagnosis of AD, aMCI, or SCD. Of those 180 patients, 7 had died by the start of this study, 15 were deemed ineligible (due to a change in diagnosis or failing the inclusion/exclusion criteria), 3 patients subsequently recorded a research 'opt-out' decision and therefore could not be approached about participation in this study, and 7 patients moved out of area. The invitation letter to participate in the study was sent to the remaining 148 patients. Of these, 25 declined to participate and 44 did not respond to the invitation letter or to follow-up telephone calls. Seventy nine patients consented to participate in the study and provided at least partial information at 3-year follow-up (Fig. 9).

3.1.1.1 Demographic data

Table 5. Demographic data of patients recruited to study and those who declined/did not respond to study invitation

Demographic variable	**Study participants n=79**	**Patients who declined participation or did not respond to study invitation n=69**	**p value of statistical difference between the groups**
Age in years			
Mean	76.7 (7.14)	76.75 (8.44)	p=0.972
Range	52-89	51-92	
Median	78	79	
Sex			
Male	44 (55.7%)	42 (60.9%)	p=0.525
Female	35 (44.3%)	27 (39.1%)	
Ethnicity			
White British	74 (93.7%)	65 (94.2%)	p=0.893
Asian	2 (2.5%)	3 (4.3%)	
Black	2 (2.5%)	1 (1.4%)	
Other white	2 (2.5%)		
Other ethnic group	1 (1.3%)		

Table 6. Age variance in AD vs non-AD groups.

Age at baseline (number of male and female participants)	mean	SD	p
AD (n=53, M=25, F=28)	78.3	7.04	0.004
Non-AD (n=26, M=19, F=7)	73.5	6.36	

SD - standard deviation, AD - Alzheimer's disease, M - male, F - female

One hundred and forty-eight patients were invited to participate in the study. Of those, 79 were recruited, 25 declined to participate and we had no response from 44 invited patients. The 79 participants included 44 men and 35 women. Mean age was 76.7 years (SD 7.14), ranging from 52 to 89 at the time of the baseline assessment. Almost all participants were white British (n=74, 94%). There were 2 participants (2.5%) each in Asian and 'other white' categories, and 1 participant's ethnicity was recorded as 'other ethnic group' (1%). There were no differences in the mean age, gender or ethnicity between the study participants and the patients who were invited to the study but who declined or did not respond to the invitation (Table 5).

People with a diagnosis of AD at follow-up (n=53) as compared with people who had a non-dementia diagnosis (non-AD, n=26) were older (mean age 78 and 74 respectively, t-test, p=0.004, Table 6), this difference reached statistical significance with p = 0.004.

3.1.1.2 Residence status across study duration

At baseline, all participants lived in their own home. They either lived alone and independently (n=18, 22.8%), or with someone else living there or coming to provide care during the day (n=61, 77.2%). At follow-up, the majority of participants lived at home, including those living alone (n=12, 15.2%) but with a higher proportion living with family members (n=55, 69.6%) or live-in carers (n=7, 8.9%). Five participants (6.3%) lived in a care home at the time of follow-up (Table 7, Fig. 10). All participants who had a live-in carer or were in a care home had an AD diagnosis at follow-up (Table 8).

Table 7. Residence status at baseline and follow-up

	Living alone (%)	Living with family or care visits (%)	24h live-in carer (%)	Living in care home (%)
Baseline	18 (22.8%), M=6, F=12	61 (77.2%), M=38, F=23	0	0
Follow-up	12 (15.2%) M=4, F=8	55 (69.6%), M=36, F=19	7 (8.9%), M=2, F=5	5 (6.3%), M=2, F=3

M - male, F - female

Figure 12. Residence at baseline and follow-up

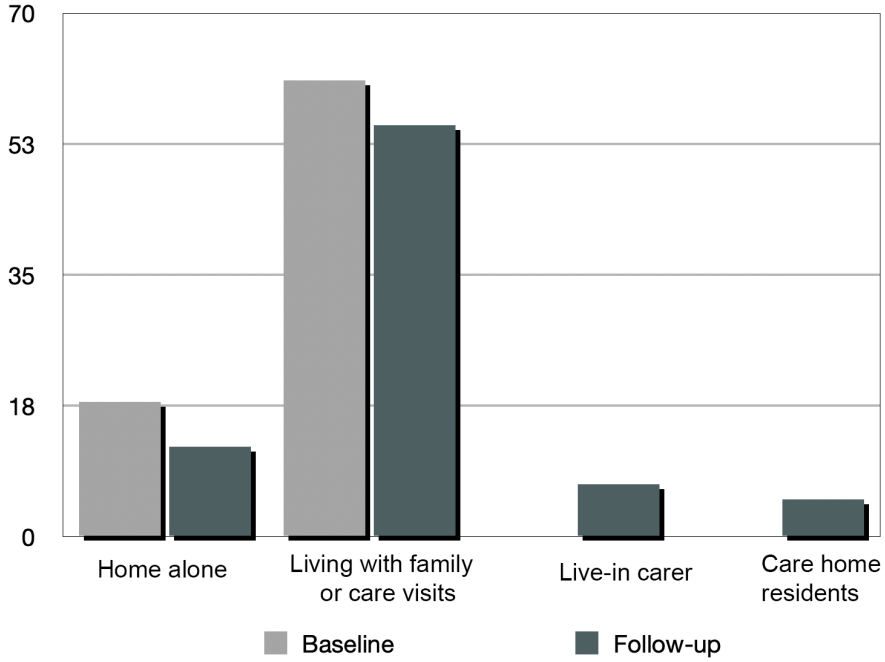


Table 8. Residence status comparison between AD vs non-AD group

Residence baseline	AD	non-AD
Living alone	12	6
Living with family/receiving care visits	41	20
Residence follow-up		
Living alone	6	6
Living with family/care visits	35	20
Live-in carer	7	0
Care home	5	0

AD - Alzheimer's disease

3.1.1.3 Educational background

This variable was captured through recording the age of leaving full time education. The mean age at which participants left full time education was 17.0 (range 14-24, SD 2.50). There was a small, non-significant difference between men and women, with the mean age of leaving full time education of 17.4 for men and 16.5 for women (SD 1.96, p=0.100).

There was no statistically significant difference in years of education between participants who had a diagnosis of AD at follow-up (n=53) as compared to those without a dementia diagnosis (non-AD group, n=26) (Table 9).

Table 9. Age of leaving full time education

Age left FT education	Mean	Range	SD	t-test
Total sample (n=79)	17.1	14-24	2.46	
Male (n=44)	17.4	14-24	2.76	p=0.117
Female (n=35)	16.5	14-21	1.96	
AD (n=53)	16.8	14-24	2.20	p=0.353
Non-AD (n=26)	17.4	14-24	2.90	

FT - full time, SD - standard deviation, AD - Alzheimer's disease, non-AD - no diagnosis of Alzheimer's disease

3.1.2 Diagnostic categories

At baseline, most participants had a diagnosis of aMCI (n=42), followed by AD (n=29) and by those who had subjective memory decline with no obvious objective cognitive impairment (n=8).

At follow-up, as expected, the number of participants with AD increased to 53. Nineteen participants met the criteria of MCI and 7 of SCD (Table 10). Thus, 24 (48.0%) of participants without a dementia diagnosis at baseline 'converted' to AD at 3 year follow-up. For the purpose of analyses, those participants without the diagnosis of dementia at follow-up were grouped together as 'non-AD' group. In the whole cohort, 54 (68.4%) participants retained the same diagnosis at follow-up and 25 (31.6%) changed diagnostic category (usually from aMCI to AD but also from SCD to AD or aMCI).

Table 10. Diagnostic categories at baseline and follow-up

Diagnosis	Baseline n (%)	Follow-up n (%)
AD	29 (36.7)	53 (67.1)
aMCI	42 (53.2)	19 (24.1)
SCD	8 (10.1)	7 (8.9)
Non-AD (SCD + aMCI)	50 (63.3)	26 (33.0)
Total	n = 79, 100%	

AD - Alzheimer's disease, aMCI - amnestic mild cognitive impairment, SCD - subjective cognitive decline

3.1.3 Cognitive performance

Table 11. Cognitive performance - descriptive statistics

Cognitive test/domain	n	Mean	Median	Min	Max	SD
ACE-R total BL	**79**	**82.4**	**86**	**53**	**97**	**10.30**
A/O baseline	75	16.9	17	10	18	1.67
Memory baseline	75	17.4	18	4	26	5.44
Fluency baseline	75	9.3	10	1	13	2.60
Language baseline	75	24.3	25	11	26	2.46
V/S baseline	75	14.9	16	9	16	1.69
MMSE baseline	78	27.2	28	16	30	2.49
ACE-R total follow-up	**69**	**75.0**	**80**	**18**	**98**	**20.12**
A/O follow-up	69	15.4	17	5	18	3.64
Memory follow-up	69	16.0	16	0	26	6.78
Fluency follow-up	69	8.0	9	0	14	3.66
Language follow-up	69	22.0	25	2	26	5.69
V/S follow-up	69	13.7	15	4	16	3.03
MMSE follow-up	72	24.1	26	2	30	6.26

n - number of participants with measured variable, ACE-R - Addenbrooke's Cognitive Examination - Revised, A/O - attention & orientation, V/S - visuospatial skills, SD - standard deviation

The average total ACE-R score at baseline was 82.4, this was 75.0 at follow-up up, a change of -7.4 points (9%). Within the cognitive domains of ACE-R, the biggest change in performance was observed in the domain of verbal fluency (14%), and the smallest difference was observed in memory sub-scale (8%) (Table 12).

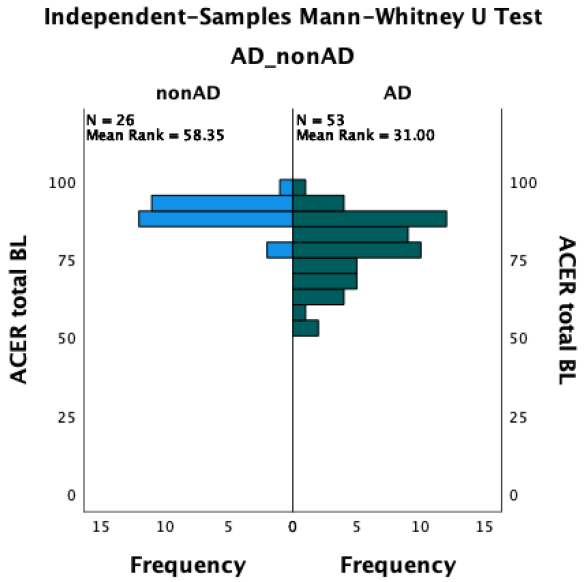
Table 12. Cognitive performance change in mean ACE-R score

	ACE-R total	A/O	MEM	Verbal fluency	Lang.	V/S	MMSE
Baseline	82.4	16.9	17.4	9.3	24.3	14.9	27.2
Follow-up	75.0	15.4	16.0	8.0	22.0	13.7	24.1
difference (%)	-7.4 (8.9%)	-1.5 (8.9%)	-1.4 (8.0%)	-1.3 (14%)	-2.3 (9.5%)	-1.2 (8.1%)	-3.1 (11.4%)

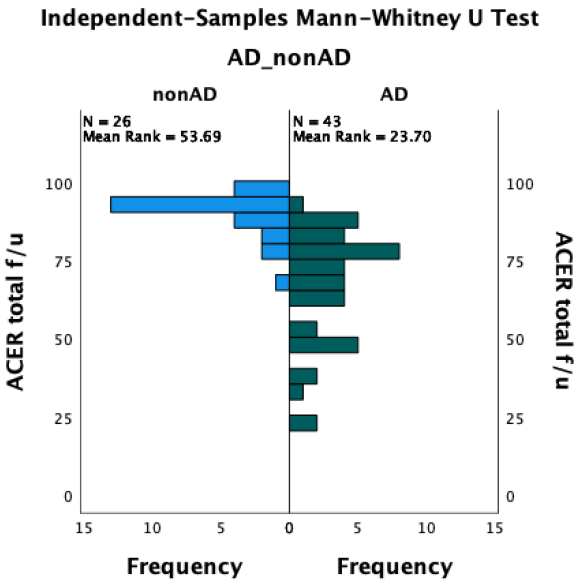
ACE-R, - Addenbrooke's Cognitive Examination-Revised, A/O - attention & orientation, MEM - memory, Lang. - language, V/S - visuospatial skills, MMSE - Mini-Mental State Examination

Figure 13. Distribution in ACE-R performance at baseline (left) and follow-up (right)

Between-group differences in ACE-R at baseline



Between-group differences in ACE-R at follow-up



■ Non-AD group, ■ AD group, ACE-R - Addenbrooke's Cognitive Examination - Revised

3.1.3.1 Cognitive performance differences between groups of participants with AD vs non-AD diagnosis at follow-up

At baseline, the majority of participants (n=50, 63.2%) did not have a diagnosis of dementia. The clinical criteria for the diagnosis of Alzheimer's dementia were met by 29

(36.7%) participants. However, at follow-up, 53 participants (67.1%) met NIA-AA diagnostic criteria for Alzheimer's dementia (McKhann et al., 2011) whilst 26 (32.9%) had a non-AD diagnosis (aMCI, n=19, and SCD, n=7). Participants were divided into two groups based on their diagnostic category at follow-up: those that met the diagnostic criteria for Alzheimer's dementia (AD group) and those who did not (non-AD group, i.e. those diagnosed with aMCI or SCD, Table 10). At baseline, there was a statistically significant difference between the two groups in the distribution of cognitive performance scores on total ACE-R score (Fig.11) and its domains of memory ($p<0.001$) and visuospatial skills ($p=0.044$), as well as in MMSE score ($p<0.001$, t-test). As expected, at follow up there was a statistically significant difference between groups in ACE-R (Fig. 11) and all its domains (Table 13).

Table 13. Group difference between cognitive performance baseline and follow-up

group		ACE-R baseline	ACE-R follow-up	p
Non-AD	mean	89.8	90.5	<0.001 (t-test)
	median	90.0	92.5	
AD	mean	81.2	65.7	<0.001 (t-test)
	median	82.0	71.0	

ACE-R - Addenbrooke's Cognitive Examination - Revised

3.1.4 Performance in activities of daily living

Descriptive statistics for scores on total BADLS and its four factors are presented in Table 14 (baseline) and 15 (follow-up). As predicted, the BADLS scores at follow up were higher in the whole sample (indicating greater impairment) with the total score range between 0 and 53 (mean 12.7, median 9).

Table 14. BADLS baseline - descriptive statistics (n=78)

	Min	Max	Mean	Median	SD
BADLS total	0	20	2.9	1	4.60
IADL	0	9	1.2	0	1.92
Self-care	0	9	0.3	0	1.23
Orientation	0	8	1.1	0	2.02
Mobility	0	2	0.2	0	0.59

BADLS - Bristol Activities of Daily Living, IADLS - instrumental activities of daily living, SD - standard deviation

Table 15. BADLS follow-up - descriptive statistics (n=75)

	Min	Max	Mean	Median	SD
BADLS total	0	53	12.7	9	12.89
IADLS	0	19	5.4	4	5.33
Self-care	0	18	2.2	0	3.98
Orientation	0	12	4.4	4	3.73
Mobility	0	6	0.7	0	1.37

BADLS - Bristol Activities of Daily Living, IADLS - instrumental activities of daily living, SD - standard deviation

The biggest change from baseline to follow up was in the factor of instrumental ADLs, and orientation, with a change of median from 0 to 4 (Tables 15 and 16).

Table 16. BADLS change

	Mean	Median
BADLS total	9.8	8
IADLS	4.2	4
Self-care	1.9	0
Orientation	3.3	4
Mobility	0.4	0

BADLS - Bristol Activities of Daily Living, IADLS - instrumental activities of daily living, SD - standard deviation

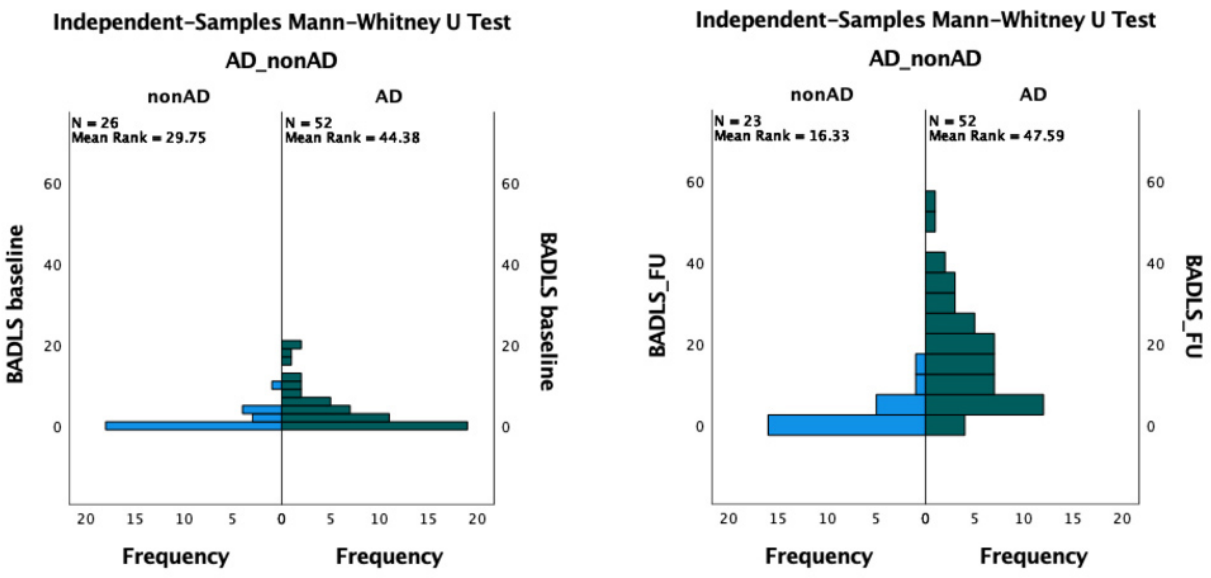
As described in chapter 2, changes in ADL performance were dichotomised to represent ‘stable’ or 'slow’ ADL decline, (9 point or less difference between follow-up and baseline measurement) and ‘rapid’ decline (15 or more points difference between follow-up and baseline BADLS score). Following this rule, over twice as many participants remained in the stable/slow decline category (n=44) as compared to those who deteriorated more (n=21). Fourteen participants could not be classified to any of those categories: 5 of them had either a baseline or a follow-up BADLS score missing, and 9 had BADLS change values falling between 10 and 14 (Table 17).

Table 17. BADLS change: fast and slow decline

	n	range (min, max)	mean	median	SD
BADLS change total	74	54 (-1, -53)	9.54	4	10.65
stable or slow decline	44	10 (-1, 9)			
rapid decline	21	38 (15, -53)			
missing total	14				

BADLS - Bristol Activities of Daily Living, IADLS - instrumental activities of daily living, SD - standard deviation

Figure 14. The distribution of BADLS scores at baseline (left) and follow-up (right) between AD and non-AD group



■ Non-AD group, ■ AD group

There was a statistically significant difference ($p<0.05$) between baseline BADLS total, IADL, and orientation scores, but not baseline scores in self-care or mobility. At follow

up, the statistically significant difference between groups was observed in total BADLS score as well as in IADL, self-care, orientation but not in mobility. The comparison and distribution of BADLS scores at baseline and follow-up are presented in Table18 and Figure 12 (Table 18, Fig. 12). The data was not normally distributed, therefore non-parametric test (Mann-Whitney U test) was used to compare the results.

Table 18. Comparison of BADLS scores at baseline and follow up in AD vs non-AD group

BADLS domain	**Mann-Whitney U test p value**
BADLS baseline*	0.04
IADL baseline *	0.013
Self-care baseline	0.244
Orientation baseline *	0.003
Mobility baseline	0.954
BADLS follow-up *	<0.001
IADL follow-up*	<0.001
Self-care follow-up *	<0.001
Orientation follow-up *	<0.001
Mobility follow-up	0.237

BADLS - Bristol Activities of Daily Living, IADLS - instrumental activities of daily living, SD - standard deviation, * denotes statistical significance

3.1.5 Risk factors and co-morbidities

The clinical history taken at baseline assessment included presence of comorbidities and risk factors for dementia disorders, such as hypertension, type 2 diabetes, ischaemic heart disease, atrial fibrillation and hypercholesterolaemia. The majority of participants (n=59, 74.7%) had at least one comorbid condition. The most frequent co-morbidity

was hypertension, present in nearly half of participants (n=39, 49.4%), followed by hypercholesterolaemia (n=18, 22.7%), type 2 diabetes (n=12, 15.2%), ischaemic heart disease (n=11, 13.9%) and atrial fibrillation (n=9, 11.4%) (Table 19).

Table 19. Frequencies of risk factors and comorbidities

Risk factor	**Number of participants with condition**	**percentage**
Hypertension	39	49.4%
Hypercholesterolaemia	18	22.7%
Type 2 diabetes	12	15.2%
Ischaemic heart disease	11	13.9%
Atrial fibrillation	9	11.4%
at least 1 of the above	59	74.7%

BADLS - Bristol Activities of Daily Living, IADLS - instrumental activities of daily living, SD - standard deviation, * denotes statistical significance (p values in bold)

Table 20 presents the prevalence of risk factors in AD as compared with non-AD group.

The prevalence of hypertension, and ischaemic heart disease or combined risk factors was proportionally higher in the AD group, whilst hypercholesterolaemia, type 2 diabetes and atrial fibrillation was more prevalent in the non-AD group. These differences were not statistically significant (Pearson Chi-Square >0.05).

Table 20. Frequencies of risk factors and comorbidities per group

Risk factor	AD (%)	non-AD (%)	significance (Pearson Chi-Square)
HT	28 (52.8%)	11 (42.3%)	NS
Hypercholesterolaemia	11 (20.7%)	7 (26.9%)	NS
Type 2 diabetes	6 (11.3%)	6 (23.0%)	NS
Ischaemic heart disease	8 (15.0%)	3 (11.5%)	NS
Atrial fibrillation	4 (7.5%)	5 (19.2%)	NS
At least 1 of the above	41 (77.3%)	18 (69.2%)	NS

AD - Alzheimer's disease, NS - not statistically significant

3.1.6 Clinical brain imaging findings

All participants' MRIs were reviewed for the clinical purpose of aiding the diagnostic process by a consultant neuroradiologist. The descriptive reports included information about hippocampal atrophy, presence and grade of microvascular disease and large vessel disease, as well as presence and number of microhaemorrhages.

3.1.6.1 Small vessel disease

The most consistent imaging finding was presence of small vessel disease, which was found in a majority of participants (n=59, 74.6%). In most cases, the severity of small vessel disease was mild, grade 1 on the Fazekas scale (Wahlund et al., 2001) (n=37, 46.8% of the total cohort, 62.7% of those with small vessel disease). Twenty-two participants with small vessel disease had it graded as moderate, with a Fazekas score of 2 (n=22, 27.8% of total cohort and 37.2% of those with small vessel disease) (Table 21).

Table 21. Prevalence and severity of small vessel disease

Small vessel disease	none	present	mild	moderate
Total n=79	20	59	37	22
AD n=53	12	41	23	18
Non-AD n=26	8	18	14	4

AD - Alzheimer's disease

When observing the prevalence of small vessel disease in the group of people with a non-AD diagnosis at follow-up, it was present in 18 participants (69.2% of the non-AD sample), with the majority of those having a mild severity of small vessel disease (n=14, 53.8% of non-AD cohort and 77.7% of non-AD group with small vessel disease). Only 4 participants (15.3% of non-AD sample and 22.2% of non-AD group with small vessel disease) had moderate small vessel disease. In the group of people with AD diagnosis at follow-up, 41 participants had small vessel disease at baseline (77.3%). Of those, 23 participants (43.3% of the AD sample, 56.0% of those with small vessel disease) had a mild degree and 18 (33.9% of the total AD sample and 44% of those with AD and small vessel disease) a moderate degree of small vessel disease. Presence of small vessel disease of any severity was associated with age, with a squared coefficient of 0.52 (52% of variance explained by age).

3.1.6.2 Hippocampal atrophy

Hippocampal atrophy was reported in less than a quarter of participants (17 participants, 21.5%). Of those,13 (76.4% of those with hiccopampal atrophy) had a diagnosis of AD at follow-up (Table 22). Most participants (n=62, 78.5%) did not have evidence of hippocampal atrophy on volumetric brain imaging. Of those, 40 (64.5%) participants had an AD diagnosis at follow-up. The odds ratio (OR) for the presence of hippocampal atrophy, as observed at baseline, in people with the diagnosis of AD at follow-up was 1.8 (95% CI 0.52-6.15). Odds ratio represents the ratio between the odds of an occurrence (diagnosis of AD) when a certain condition is true (presence of hippocampal atrophy),

divided by the odds of the same occurrence (diagnosis of AD) when the condition is not true (no hippocampal atrophy). Here the OR would suggest a 1.8 fold increased risk of AD diagnosis in participants with hippocampal atrophy reported on visual rating.

Table 22. Prevalence of hippocampal atrophy in the study cohort

Hippocampal atrophy	whole cohort n=79	AD n=53	non-AD n=26
present	17	13	4
absent	62	40	22

AD - Alzheimer's disease

3.1.6.3 Microhaemorrhages

Only 8 participants (10.1% of the total group of 79) had evidence of microhaemorrhages in their baseline MRI, 5 only had a solitary haemorrhage and 3 had multiple haemorrhages.

3.1.7 Neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed using the NPI and collected only at follow-up, as the NPI was not a part of routine pathway in memory assessment clinic and so was not completed at baseline. The NPI is a scale completed by the carer, therefore it was not available for participants who did not have a study partner.

The NPI data was collected for 75 participants (M=40, F=35), mean age 77 (range 52-89). There was variability in how many participants scored above 0 on a particular item. Most common item, reported for nearly half of participants, was irritability (n=36, 48%), followed by depression (n=33, 44%) and symptoms of agitation, anxiety, apathy, and appetite change, each reported for 27 (36%) participants. Only one participant was reported to show elation, with the score of 3 on NPI item (Table 23).

Table 23. Number of participants reporting symptoms and mean/median scores

NPI item in the order of frequency of participant reporting	n (%) of participants reporting symptom	NPI score range in domain	Mean (median) NPI score in domain	Mean (median) NPI score in domain in participants reporting symptoms
Irritability	35 (47)	0-8	1.02 (0)	2 (2)
Depression	33 (44)	0-8	1.29 (0)	3 (2)
Agitation	27 (36)	0-8	1.4 (0)	3.8 (3)
Anxiety	27 (36)	0-12	1.22 (0)	3.4 (3)
Appetite/ eating change	26 (35)	0-12	1.24 (0)	3.4 (3)
Apathy	26 (35)	0-8	1.12 (0)	3 (3)
Sleep	25 (33)	0-9	1.25 (0)	3.6 (3)
Aberrant motor activity	18 (24)	0-12	0.88 (0)	3.5 (
Delusions	14 (19)	0-12	0.64 (0)	3.4 (3)
Disinhibition	12 (16)	0-3	0.3 (0)	2 (2)
Hallucinations	6 (8)	0	0.16 (0)	2 (2)
Elation	1 (1)	3	0.04 (0)	3

NPI - Neuropsychiatric Inventory

3.1.7.1 NPI comparison between participants with AD and non-AD diagnosis at follow-up

There was a statistically significant difference (Mann-Whitney U test) in the distribution of NPI scores between groups (AD vs non-AD) in total NPI, NPI with no sleep/appetite,

as well as in Hyperactivity and Apathy sub-syndromes. For single items, statistically significant differences between groups was observed in delusions, agitation, apathy and appetite/eating habits. There was no difference in NPI score distribution for Psychosis and Affective sub-syndromes. In single items, there was no difference in hallucinations, depression, anxiety, elation (although only 1 study partner reported score > 0 on the latter). Table 24 presents the percentage of participants reporting scores >0 on NPI items in AD vs non-AD group.

Table 24. Number of participants with score > 0 on NPI items

	AD (%)	**non-AD (%)**	**total**
Delusions	14 (27%)	0	14 (19%)
Hallucinations	5 (10%)	1 (4%)	6 (8%)
Agitation	24 (46%)	3 (13%)	27 (36%)
Depression	23 (44%)	10 (43%)	33 (44%)
Anxiety	19 (36.5%)	8 (35%)	27 (36%)
Elation	1 (2%)	0	1 (1%)
Apathy	22 (42%)	4 (17 %)	26 (35%)
Disinhibition	10 (19%)	2 (9%)	12 (16%)
Irritability	24 (46%)	11 (48%)	35 (47%)
Aberrant motor behaviour	15 (29%)	3 (13%)	18 (24%)
Sleep and night-time behaviour	18 (35%)	7 (30%)	25 (33%)
Appetite and eating changes	23 (44%)	3 (13%)	26 (35%)

3.1.7.2 High vs low NPI burden

We dichotomised the participants into those with high (NPI over 10) and low (NPI below 9) NPS burden. The majority of participants (n=47, 62.7% of the study sample with available NPI scores) were in the low NPI group, whilst 28 (37.3%) were in the high NPI group.

A higher proportion of participants in the AD group had high NPI score as compared to non-AD group but the difference was not statistically significant (Pearson Chi-Squared) as illustrated in Table 25.

Table 25. Participants with High and Low NPI score in AD and non-AD group

	non-AD	**AD**	**Pearson Chi-Squared**
High NPI	6 (23.0%)	22 (43.3%)	p=0.181
Low NPI	17 (77.0%)	30 (56.7%)	

NPI - neuropsychiatric inventory, high NPI 10 and above, low NPI 0-9

3.2 Voxel based morphometry

This section presents the results of volumetric whole brain analysis, which focused on the correlation between regional tissue volume at baseline and the clinical variables of interest: ADL as measured by BADLS score and its change between baseline and follow-up; and neuropsychiatric symptoms, as measured by NPI score at follow-up. The analyses were performed on the whole group cohort of participants with available follow-up clinical variables (n=75, M = 40, F = 35) as well as within groups of people with the diagnosis of AD (n= 52) and non-AD (n=23). All analyses were adjusted for age, gender and whole brain volume. The results are reported with FWE correction at cluster level.

3.2.1 Correlation between regional grey matter volume and activities of daily living

We performed correlation analysis of whole brain GM volume with BADLS scores, as a measure of ADL, in the total study cohort and within AD and non-AD groups. The correlation analysis included covariates of age, sex and total brain volume. We did not find any significant clusters of correlation between regional GM volume and total BADLS score or scores in the four factors (IADL, orientation, self-care and mobility - Table 26). Furthermore, we did not find significant clusters of between-group difference when comparing participants with slow and fast ADL decline.

Table 26. Correlation analyses between BADLS measures and regional GM volume

BADLS measure	Group (n)		
	Total cohort (n=75)	AD (n=52)	nonAD (n=23)
total BADLS change (between baseline and follow-up)	NS	NS	NS
total BADLS baseline	NS	NS	NS
total BADLS follow-up	NS	NS	NS
IADL factor change (between baseline and follow-up)	NS	NS	NS
IADL factor baseline	NS	NS	NS
IADL factor follow-up	NS	NS	NS
Self-care factor change (between baseline and follow-up)	NS	NS	NS
Self-care factorbaseline	NS	NS	NS
Self-care factor follow-up	NS	NS	NS
Orientation factor change (between baseline and follow-up)	NS	NS	NS
Orientation factor baseline	NS	NS	NS
Orientation factor follow-up	NS	NS	NS
Mobility factor change (between baseline and follow-up)	NS	NS	NS
Mobility factor baseline	NS	NS	NS
Mobility factor follow-up	NS	NS	NS

BADLS - Bristol Activities of Daily Living Scale, GM - grey matter, IADL - instrumental activities of daily living, NS - not significant

3.2.2 Correlation between regional grey matter volume and neuropsychiatric symptoms

We performed correlation analyses between GM volume and NPI measures as follows:

- total NPI score
- NPI Hyperactivity sub-syndrome
- NPI Psychosis sub-syndrome
- NPI Affective sub-syndrome and
- NPI Apathy sub-syndrome, as well as in single NPI items of:
- hallucinations
- delusions
- irritability
- depression
- anxiety
- apathy
- disinhibition
- sleep and night-time behaviour change
- appetite change
- aberrant motor activity

We did not perform correlation analysis with NPI scores in the item of elation as only one participant reported scores above 0 in this domain. There were no significant clusters of correlation between regional brain volume and the scores in those domains when performed on the whole cohort of participants or in the cohort of people with non-AD diagnosis at follow-up.

When performing correlation analysis within the group of participants with the diagnosis of AD at follow-up (n=52), we found a negative correlation between regional GM volume and selected NPI measures, which are listed and further described below. A negative correlation between GM volume and NPI measures indicates that reduced regional GM volume was associated with higher severity of the specified neuropsychiatric symptom or sub-syndrome.

3.2.2.1 Correlation between regional grey matter volume and total NPI score in participants with AD diagnosis at follow-up (n=52)

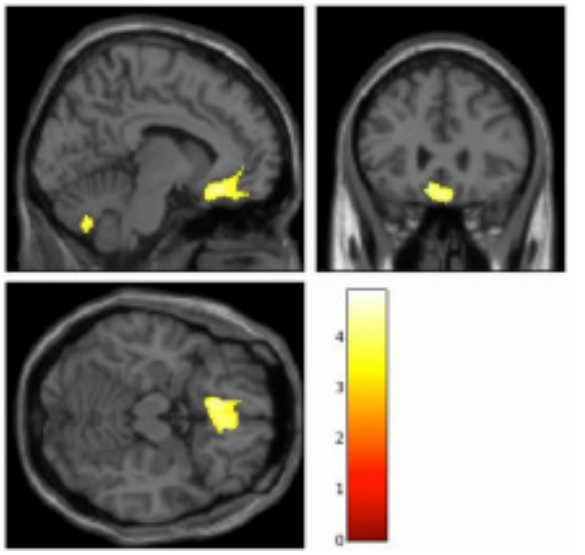
We found a significant negative correlation between total NPI score and regional GM volume in OFC (Fig. 13), as well as crus II in left and right cerebellum (Fig. 14). The significance survived correction for multiple comparisons at cluster level ($p < 0.005$ FWE corrected). Table 27 shows anatomical coordinates of cluster centres (MNI atlas).

Table 27. Cluster of correlation between regional GM volume and total NPI score

	p FWE-corrected (cluster level)	**Correlation coefficient r**	**Expected voxels per cluster**	**Coordinates of the cluster centre (x, y, z)**
Cerebellar cluster (centre in right crus II)	0.001	-0.5688	2015	10 -70 -45
OFC (cluster centre in left OFC)	0.006	-0.5257	1466	-8 27 -16
Cerebellar cluster (centre in left crus II)	0.045	-0.5080	829	-28 -72 -44

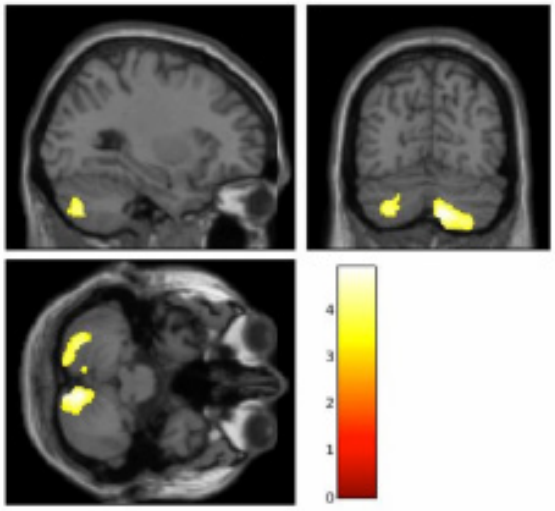
NPI - Neuropsychiatric Inventory, GM - grey matter, OFC - orbitofrontal cortex

Figure 15. Negative correlation between total NPI and regional GM volume in OFC



NPI - neuropsychiatric Inventory, GM - grey matter, OFC - orbitofrontal cortex

Figure 16. Negative correlation between total NPI and regional GM volume in crus II (cerebellum)



NPI - Neuropsychiatric Inventory, GM - grey matter

3.2.2.2 Correlation between regional grey matter volume and NPI Psychosis sub-syndrome in participants with AD diagnosis at follow-up at (n=52)

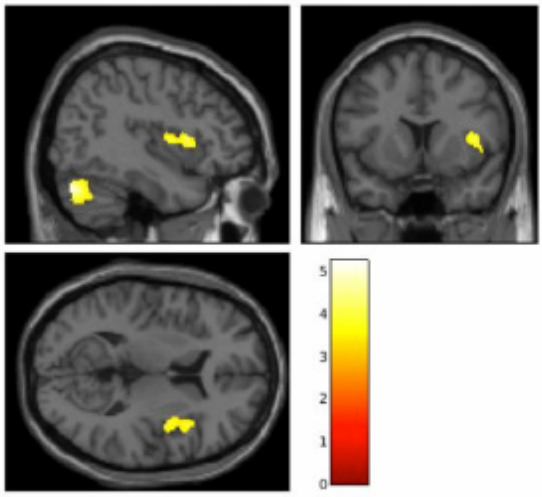
We found a negative correlation between the NPI Psychosis sub-syndrome and GM volume of the cerebellum (significant after FWE correction at cluster level) and the right frontal cortex (BA 44); the latter cluster only approached statistical significance at cluster level following FWE correction (Fig 15). Table 28 shows MNI coordinates of clusters' centre.

Table 28. Clusters of correlation between regional GM volume and NPI Psychosis

	p FWE-corrected (cluster level)	Correlation coefficient r	Expected voxels per cluster	Coordinates of the cluster centre (x, y, z)
Cerebellar cluster (centre in right crus)	0.000	-0.5961	7933	38 -78 -30
Right frontal opercular (BA 44) cluster	0.096	-0.5053	610	42 12 8

GM - grey matter, NPI - Neuropsychiatric Inventory, FWE - family wise error, BA - Brodmann area

Figure 17. Negative correlation between NPI Psychosis and GM volume in right frontal insular complex and cerebellum



NPI - Neuropsychiatric Inventory, GM - grey matter

3.2.2.3 Correlation between regional grey matter volume and NPI anxiety item in participants with AD diagnosis at follow-up (n=52)

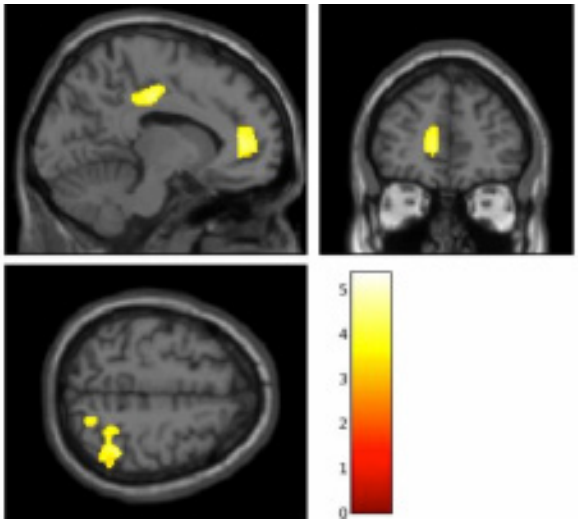
We found a negative correlation between severity in NPI anxiety item and regional GM volume in the left PCC and ACC, as well as the right superior parietal lobule and precuneus (Table 29, Fig. 16).

Table 29. Clusters of correlation between regional GM volume and NPI anxiety

	p FWE-corrected (cluster level)	Correlation coefficient r	Expected voxels per cluster	Coordinates of the cluster centre (x, y, z)
Left PCC	0.001	-0.6055	972	-6 -21 39
Right superior parietal lobule (cluster extending medially into precuneus)	0.000	-0.5544	1185	42 -46 57
Left ACC	0.003	-0.5386	778	-10 42 9

NPI - Neuropsychiatric Inventory, GM - grey matter, FWE - family wise error, PCC - posterior cingulate, ACC - anterior cingulate,

Figure 18. Negative correlation between NPI anxiety and GM volume in the left ACC and PCC and the right parietal lobule



NPI - Neuropsychiatric Inventory, GM - grey matter, ACC - anterior cingulate cortex, PCC - posterior cingulate cortex

3.2.2.4 Correlation between regional grey matter volume and NPI sleep and night-time behaviour disorder item in participants with AD diagnosis at follow-up at (n=52)

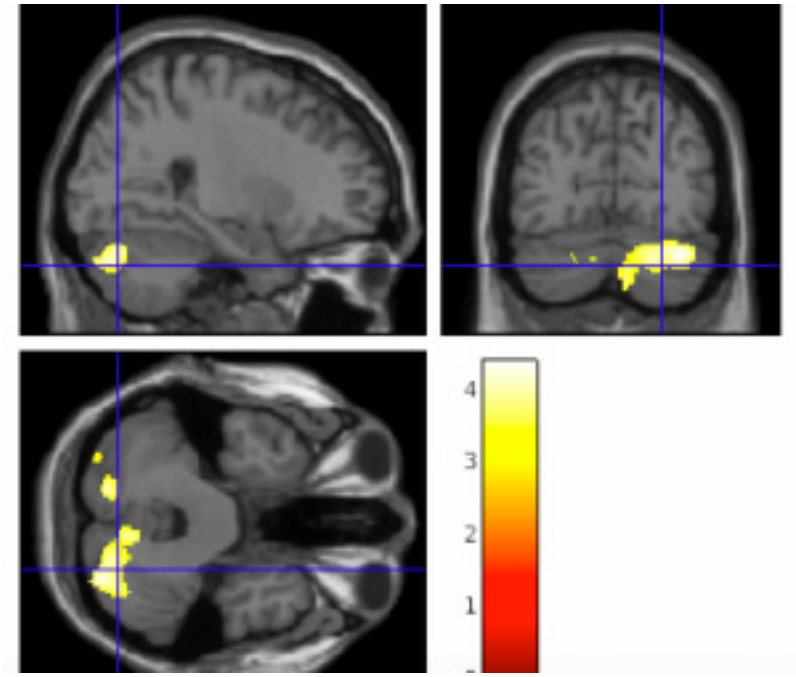
We have found negative correlation between GM volume and the severity of sleep and night-time behaviour disorder NPI item in crus I, cerebellum, bilaterally (Table 30, Fig. 17).

Table 30. Clusters of correlation between regional GM volume and NPI sleep and night-time behaviour disorder

	p FWE-corrected (cluster level)	**Correlation coefficient r**	**Expected voxels per cluster**	**Coordinates of the cluster centre (x, y, z)**
Right crus I	0.000	-0.5266	2400	36 -76 -28
Left crus I	0.007	-0.4997	639	-33 -80 -32

NPI - neuropsychiatric inventory, GM - grey matter, FWE = family wise error, N - number

Figure 19. Negative correlation between NPI sleep and nighttime behaviour disorder and GM volume in crus I, cerebellum bilaterally



NPI - Neuropsychiatric Inventory, GM - grey matter

3.3 Brain network connectivity analysis

Following the exclusion of 14 scans showing excessive head motion during pre-processing, rs-fMRI analysis was performed on a cohort of 65 participants (M = 36, F = 29, mean age 76.5).
Of those, 42 had a diagnosis of AD at follow up and 23 had a non-AD diagnosis of aMCI or SCD at follow up. We found significant correlation between network connectivity and neuropsychiatric symptoms in the group of participants with AD but not those with non-AD.

The results of brain connectivity analysis is presented separately for the following brain networks in the following sections: 3.3.1 (DMN), 3.3.2 (salience network), 3.3.3. (right frontoparietal network), and 3.3.4 (left frontoparietal network).

The p values were considered significant when lower than 0.05, with TFCE option employed as correction for multiple comparisons (Smith and Nichols, 2009).

3.3.1 Connectivity in the default mode network

There was a positive correlation between DMN connectivity and NPI scores in agitation (Table 31, Fig. 18), irritability (Table 32, Fig.19) and sleep and night-time behaviour disorder (Table 33, Fig. 20). The positive correlation denotes that stronger connectivity within the network at baseline was associated with more severe neuropsychiatric symptoms at 3-year follow-up. We also found a negative correlation between network connectivity in DMN and NPI score in the appetite and eating change item of the NPI, signifying that reduced DMN connectivity at baseline was associated with more severe changes in appetite and eating habits at 3-year follow-up in participants with AD. (Table 34, Fig. 21). There was no significant correlation between functional connectivity within this network and scores in other NPI items and sub-syndromes.

3.3.1.1 Agitation

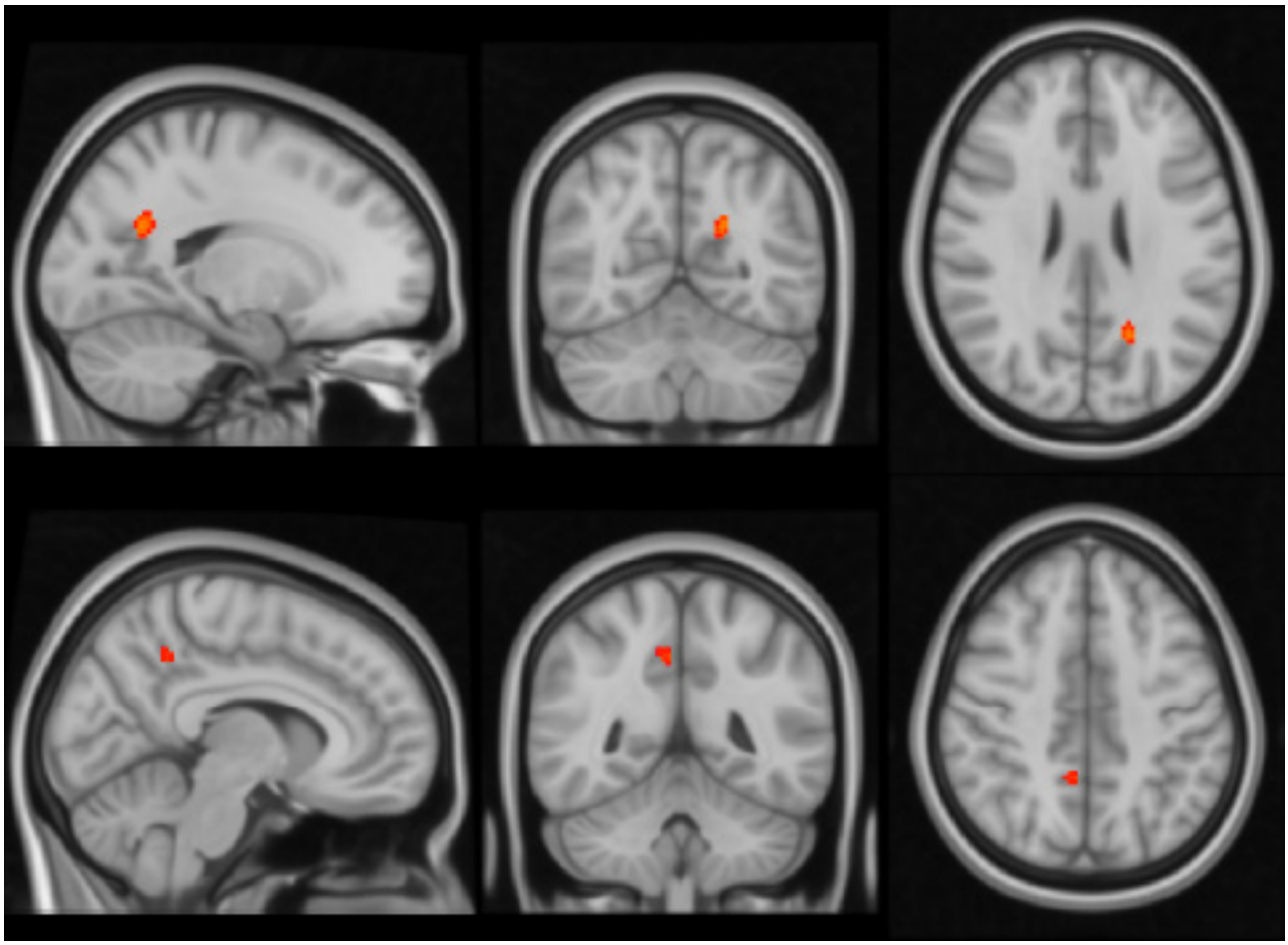
Positive correlation was found between functional connectivity in the DMN and NPI agitation score with significant clusters of peak connectivity in left and right precuneus (Table 31, Fig. 18).

Table 31. Areas of significant correlation between functional connectivity within the DMN and NPI agitation

	Cluster size	p	Coordinates (x, y, z)
Left precuneus	47	0.039	-18 -60 26
Right precuneus	18	0.043	8 -48 44

DMN - default mode network, NPI - Neuropsychiatric Inventory

Figure 20. Areas of significant correlation between functional connectivity within the DMN and NPI agitation item - left (top row) and right (bottom row) precuneus. Significant clusters (in red) are overlaid onto the SPM T1-weighted template in MNI space.



DMN - default mode network, NPI - Neuropsychiatric Inventory

3.3.1.2 Irritability

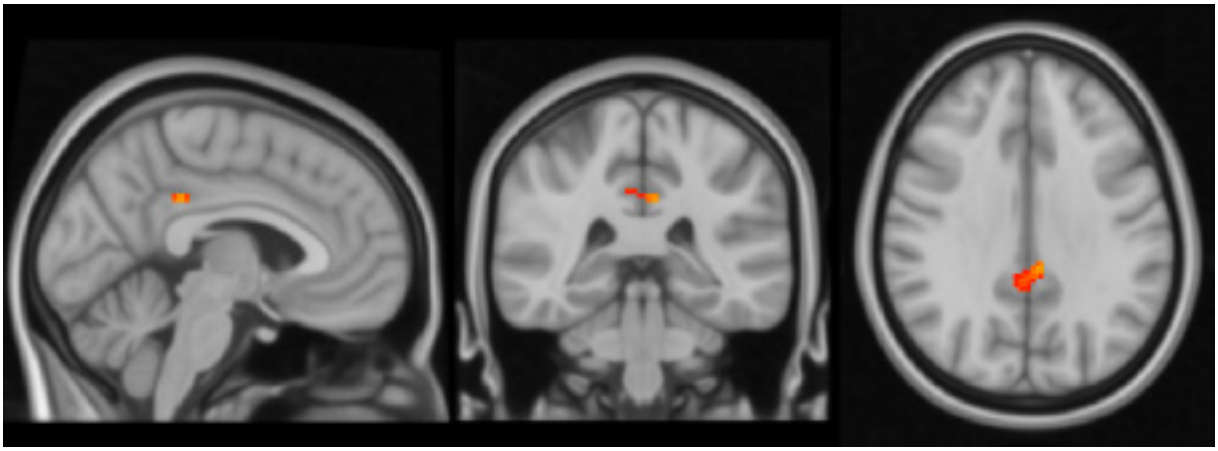
Positive correlation was found between functional connectivity in the DMN and NPI irritability score with significant clusters of peak connectivity in left and right PCC (Table 32, Fig. 19).

Table 32. Areas of significant correlation between functional connectivity within the DMN and NPI irritability domain

	Cluster size	p	Coordinates (x, y, z)
Left and right PCC	113	0.034	-4 -36 32

DMN - default mode network, NPI - Neuropsychiatric Inventory, PCC - posterior cingulate cortex

Figure 21. Areas of significant correlation between functional connectivity within the DMN and NPI irritability item - left and right PCC



DMN - default mode network, NPI - Neuropsychiatric Inventory, PCC - posterior cingulate cortex

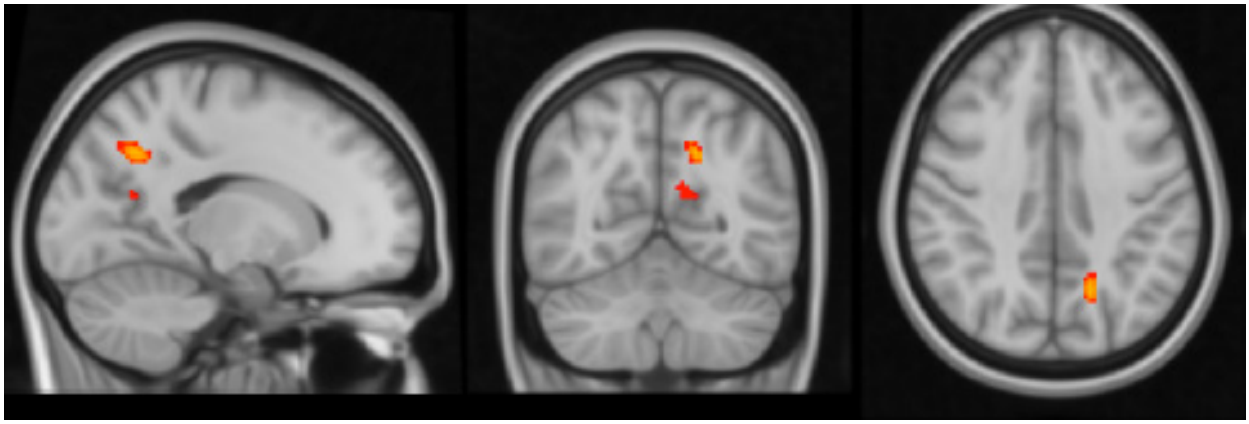
3.3.1.3 Sleep and night-time behaviour disorder

We found positive correlation between functional connectivity in the DMN and NPI sleep and night-time behaviour disorder item in the right precuneus (Table 33, Fig. 20).

Table 33. Areas of significant correlation between functional connectivity within the DMN and NPI sleep and night-time behaviour item

Brain region	Cluster size	p	Coordinates (x, y, z)
Right precuneus	77	0.025	-16 -60 38
Right precuneus	34	0.044	-12 -62 18

Figure 22. Areas of significant correlation between functional connectivity within the DMN and NPI sleep item - right precuneus



DMN - default mode network, NPI - Neuropsychiatric Inventory

3.3.1.4 Appetite and eating habits change

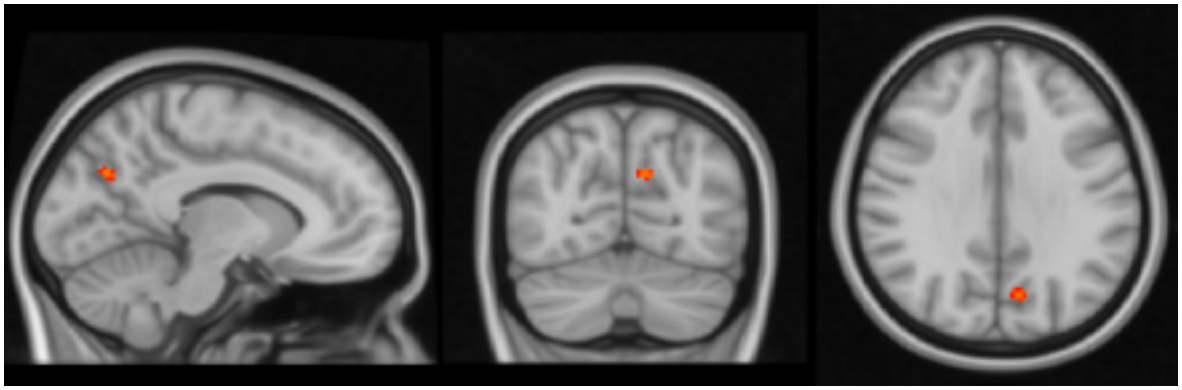
In contrast to our other findings of positive correlation within network connectivity and NPI scores, we have found negative correlation in functional connectivity within the DMN and the NPI appetite and eating habits item in the left precuneus, extending to cuneus cortex (Table 34, Fig. 21).

Table 34. Areas of significant negative correlation between functional connectivity within DMN and NPI appetite and eating habits

Brain region	Cluster size	p	Coordinates (x, y, z)
Left precuneus/ cuneus cortex	26	0.039	-10 -70 30

DMN - default mode network, NPI - Neuropsychiatric Inventory

Figure 23. Areas of significant negative correlation between functional connectivity within the DMN and NPI appetite and eating habits



DMN - default mode network, NPI - Neuropsychiatric Inventory

3.3.2 Connectivity in the salience network

We found a positive correlation between the salience network connectivity and NPI scores in the Affective sub-syndrome (Table 35, Fig. 22), agitation (Table 36, Fig.23), anxiety (Table 37, Fig. 24 and aberrant motor behaviour (Table 38, Fig. 25). There was no statistically significant correlation between functional connectivity in the salience network and other NPI sub-syndromes or items.

3.3.2.1 Affective sub-syndrome

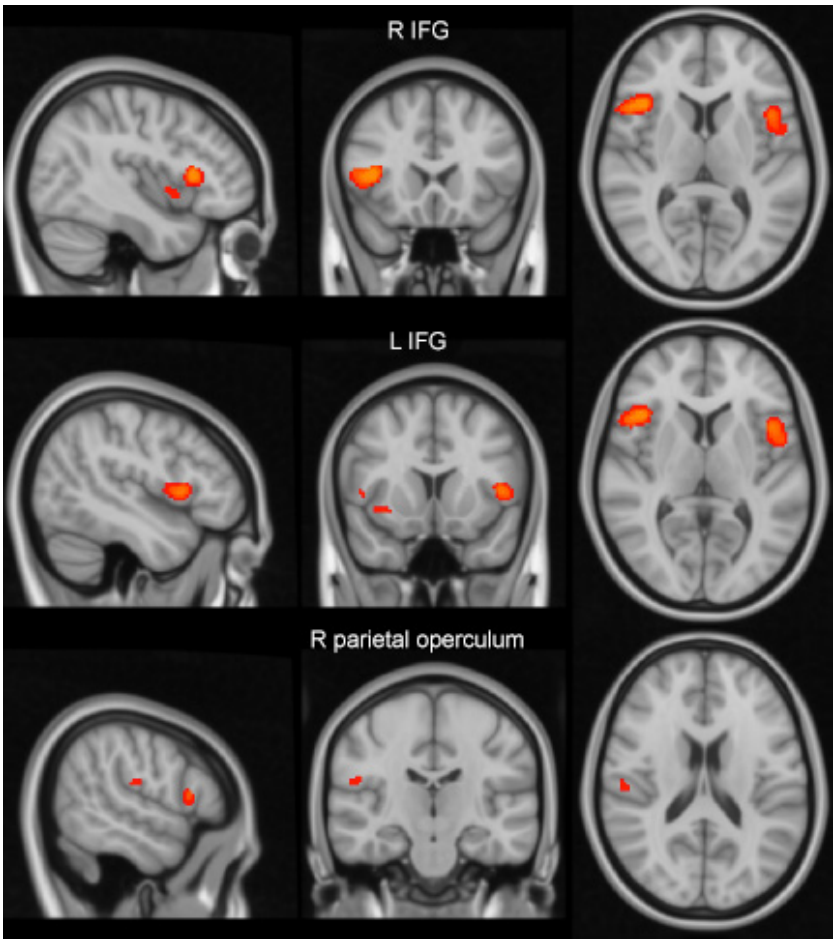
Positive correlation was found between functional connectivity in the salience network and NPI Affective sub-syndrome with significant clusters of peak connectivity in right frontal operculum, left IFG, right insula and the right parietal operculum (Table 35, Fig. 22).

Table 35. Areas of significant correlation between functional connectivity within the salience network and NPI Affective sub-syndrome

Brain region	Cluster size	p	Coordinates (x, y, z)
Right frontal operculum, IFG	357	0.036	42 20 8
Left IFG	243	0.038	-46 12 6
Right insula	87	0.042	34 10 -8
Right parietal operculum	23	0.043	56 -20 18

NPI - Neuropsychiatric Inventory, IFG - inferior frontal gyrus

Figure 24. Areas of significant correlation between functional connectivity within the salience network and NPI Affective sub-syndrome



NPI - Neuropsychiatric Inventory, R - right, IFG - inferior frontal gyrus, L - left

3.3.2.2 Agitation

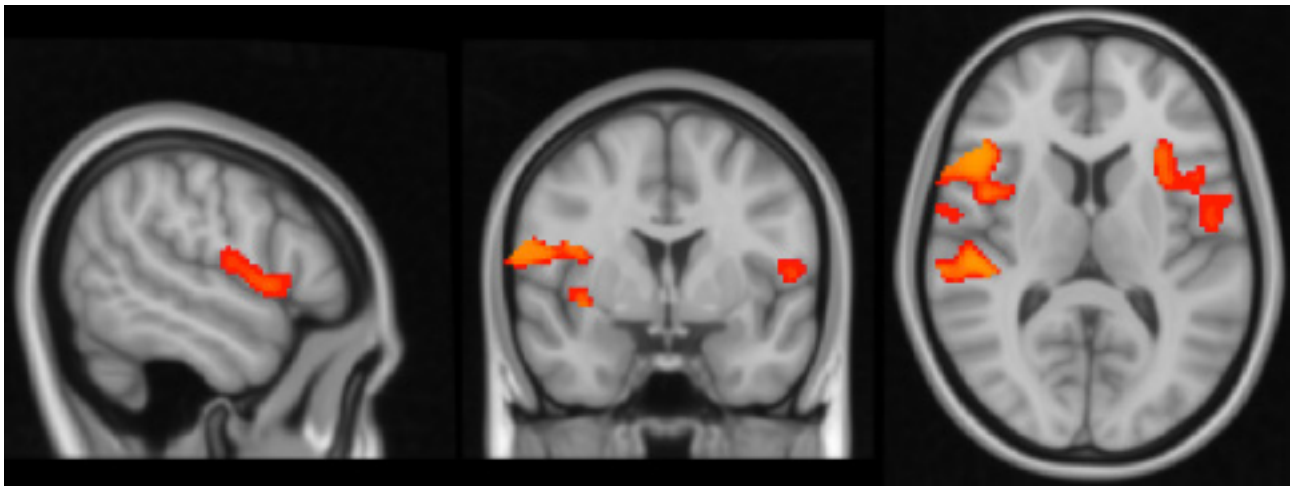
Positive correlation was found between functional connectivity within the salience network and NPI agitation item with significant clusters of peak connectivity in the right SMG/right insula as well as left frontal operculum/IFG (Table 36, Fig. 23)

Table 36. Areas of significant correlation between functional connectivity within the salience network and NPI agitation

Brain region	Cluster size	p	Coordinates (x, y, z)
Right SMG, Insula (A)	2893	0.016	50 -24 30
Left frontal operculum, IFG (B)	696	0.026	-46 12 4

NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus, IFG - inferior frontal gyrus

Figure 25. Areas of significant correlation between functional connectivity within the salience network and NPI agitation: 2 significant clusters with centre in the right SMG/insula (A) and left frontal operculum and IFG (B)



NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus, IFG - inferior frontal gyrus

3.3.2.3 Anxiety

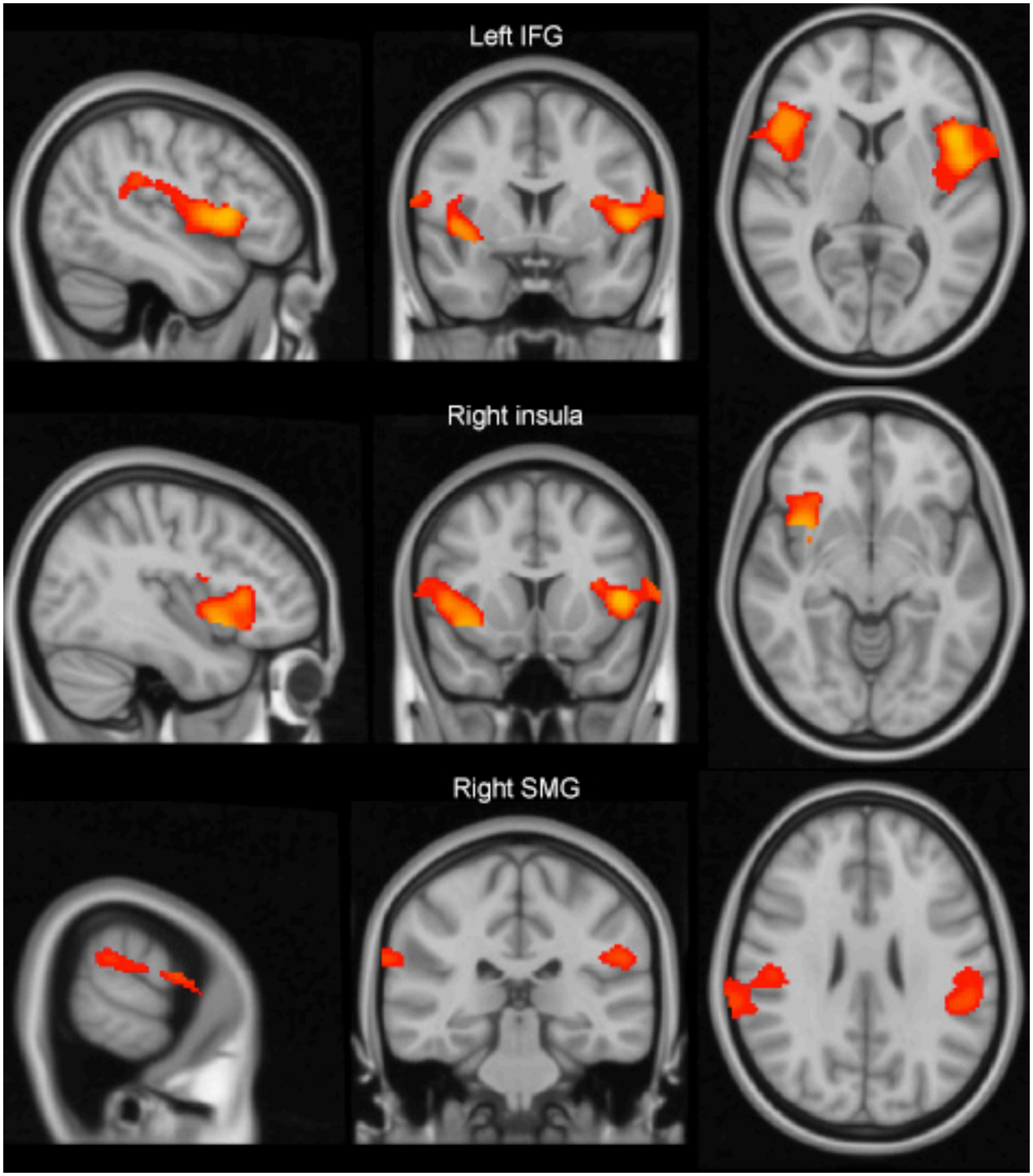
Positive correlation was found between functional connectivity within the salience network and NPI anxiety item with significant clusters of peak connectivity in the right SMG/right insula as well as left frontal operculum/IFG (Table 37, Fig. 24).

Table 37. Areas of significant correlation between functional connectivity within the salience network and NPI anxiety

Brain region	Cluster size	p	Coordinates (x, y, z)
Left IFG, opercular cortex	2429	0.029	-46 12 6
Right insula	1750	0.024	40 12 -8
Right SMG	764	0.037	72 -36 26

NPI - Neuropsychiatric Inventory, IFG - inferior frontal gyrus, SMG - supramarginal gyrus

Figure 26. Areas of significant correlation between functional connectivity within the salience network and NPI anxiety in 3 significant clusters with centres in left IFG and opercular cortex, right insula and right SMG.



NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus, IFG - inferior frontal gyrus

3.3.2.4 Aberrant motor behaviour

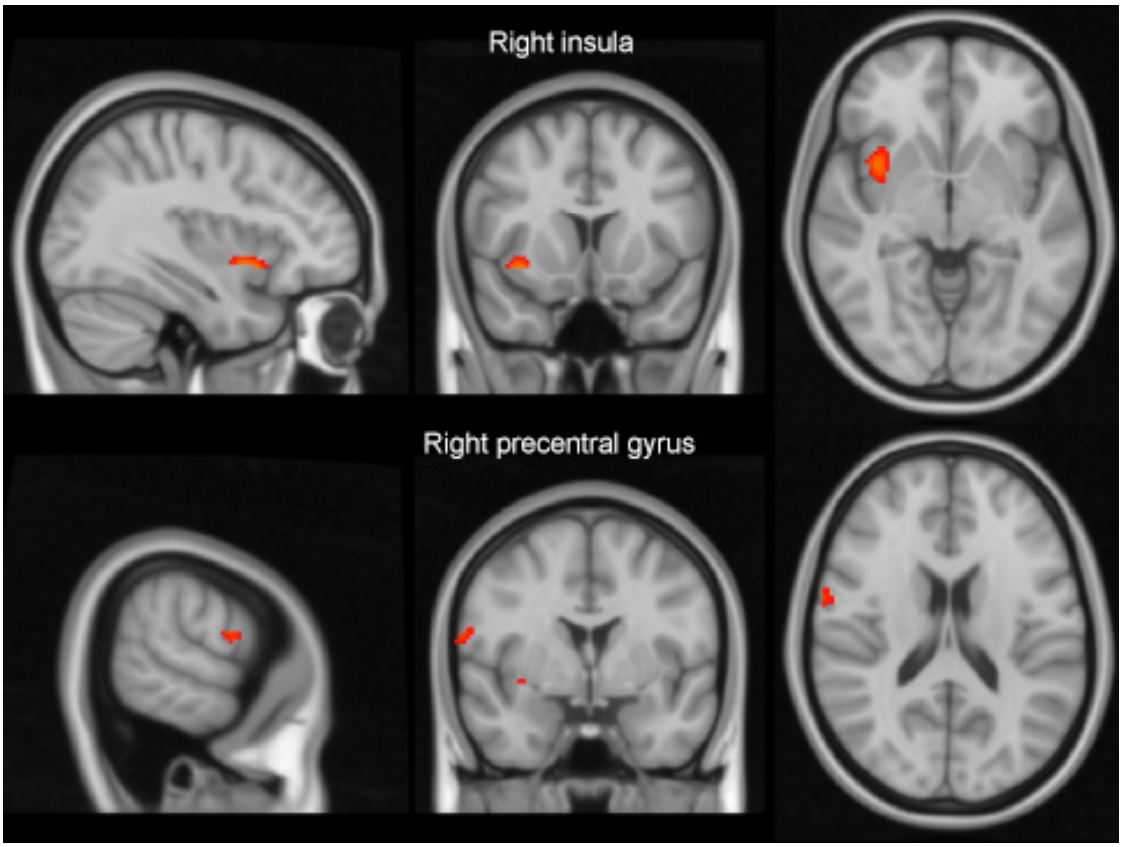
Positive correlation was found between functional connectivity within the salience network and NPI aberrant motor behaviour item with significant clusters of peak connectivity in the right insula and the right precentral gyrus (Table 38, Fig. 25).

Table 38. Areas of significant correlation between functional connectivity within the salience network and NPI aberrant motor behaviour

Brain region	Cluster size	p	Coordinates (x, y, z)
Right insula	87	0.041	36 12 -8
Right precentral gyrus	32	0.044	64 0 18

NPI - Neuropsychiatric Inventory

Figure 27. Areas of significant correlation between functional connectivity within the salience network and NPI aberrant motor behaviour - 4 significant clusters with centres in the right insula and right precentral gyrus



NPI - Neuropsychiatric Inventory

3.3.3 Connectivity in the right frontoparietal network

We found positive correlation between the connectivity in the right network and NPI scores in the total NPI (Table 39, Fig. 26), NPI Psychosis sub-syndrome (Table 40, Fig. 27), NPI Hyperactivity sub-syndrome (Table 41, Fig. 28), agitation (Table 42, Fig. 29) and NPI sleep and night-time behaviour disorder (Table 43, Fig. 30). There was no statistically significant correlation between functional connectivity in right frontotemporal network and other NPI symptoms and sub-syndromes.

3.3.3.1 NPI total

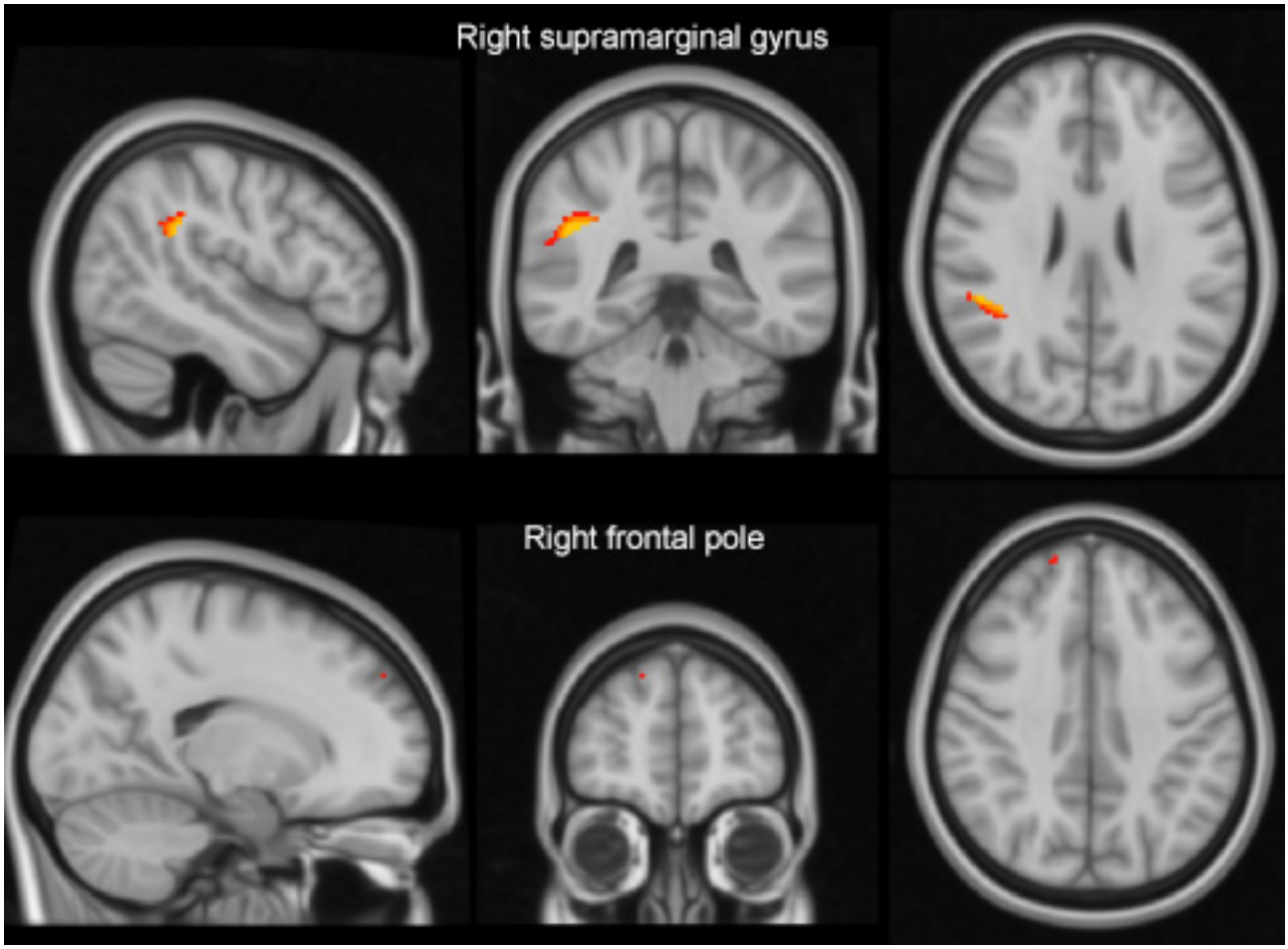
Positive correlation was found between functional connectivity within the right frontoparietal network and total NPI score with significant clusters of peak connectivity in the SMG and right frontal pole (Table 39, Fig. 26).

Table 39. Areas of significant correlation between functional connectivity within the right frontoparietal network and total NPI score

Brain region	**Cluster size**	**p**	**Coordinates (x, y, z)**
Right SMG	181	0.01	48 -40 26
Right frontal pole	5	0.049	18 52 38

NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus

Figure 28. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI total score with 2 significant clusters with peak connectivity in the right SMG and a small cluster in right frontal pole



RFP - right frontoparietal network, NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus

3.3.3.2 Psychosis sub-syndrome

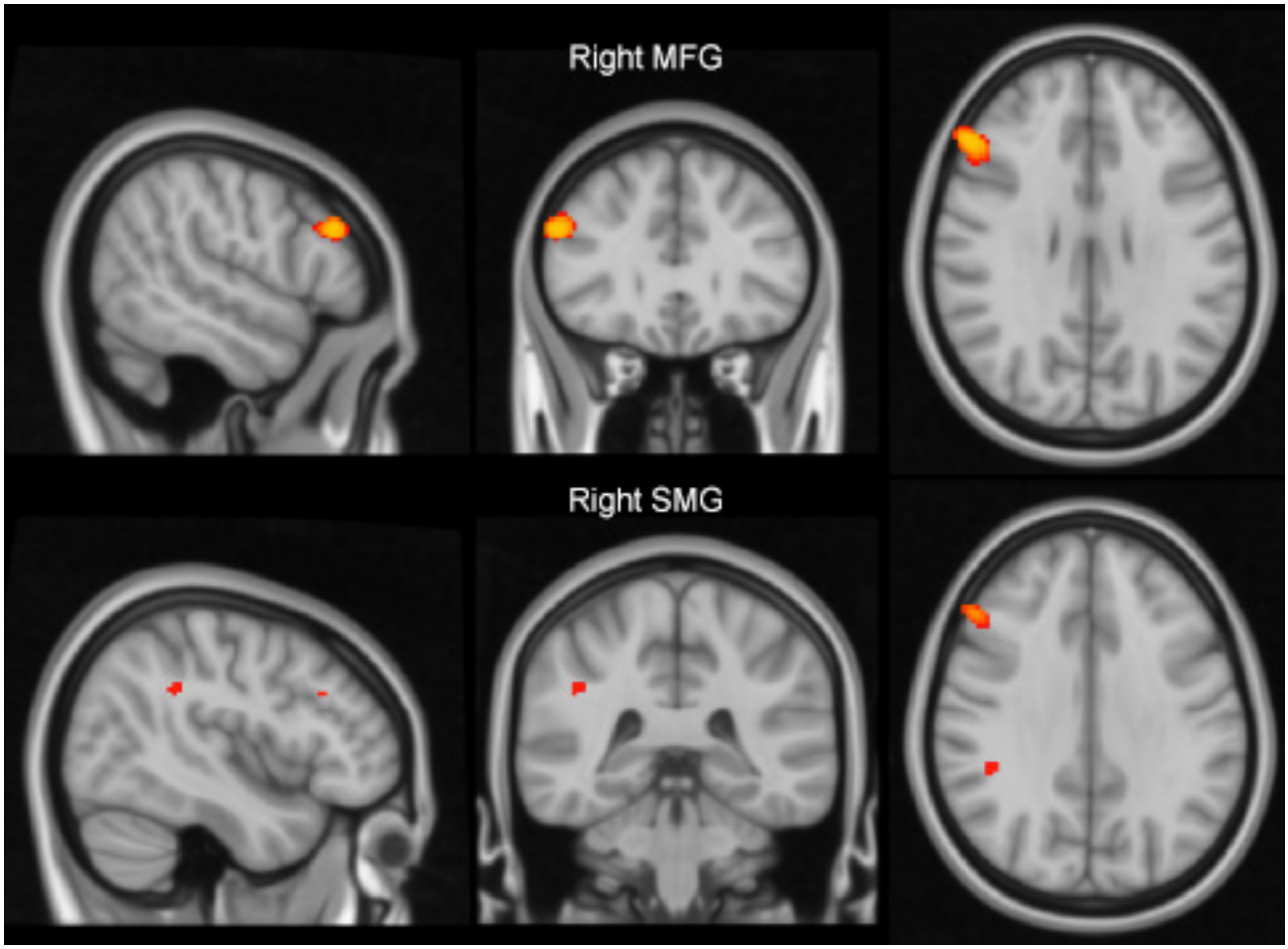
Positive correlation was found between functional connectivity within the right frontoparietal network and total NPI Psychosis sub-syndrome, with significant clusters of peak connectivity in the right MFG and right SMG (Table 40, Fig. 27).

Table 40. Areas of significant correlation between functional connectivity within the right frontoparietal network NPI Psychosis sub-syndrome

Brain region	Cluster size	p	Coordinates (x, y, z)
Right MFG	181	0.015	54 30 28
Right SMG	18	0.045	44 -38 32

NPI - Neuropsychiatric Inventory, MFG - middle frontal gyrus, SMG - supramarginal gyrus

Figure 29. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI Psychosis sub-syndrome score with 2 significant clusters with peak connectivity in the right MFG and a small cluster in the right SMG



NPI - Neuropsychiatric Inventory, MFG - middle frontal gyrus, SMG - supramarginal gyrus

3.3.3.3 Hyperactivity sub-syndrome

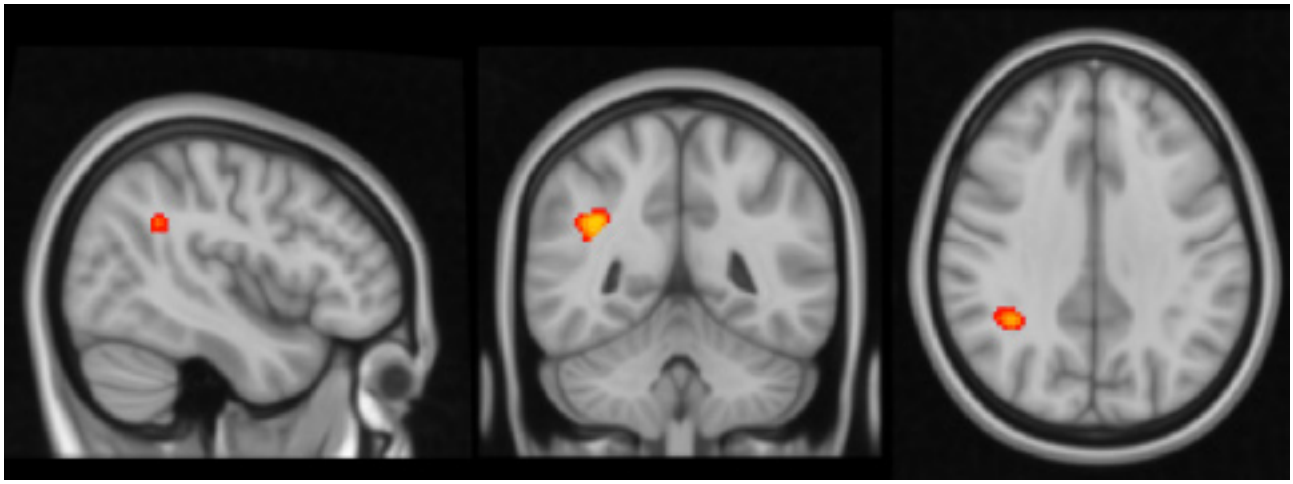
Positive correlation was found between functional connectivity within the right frontoparietal network and total NPI Hyperactivity sub-syndrome, with one significant cluster of peak connectivity in the right angular gyrus (Table 41, Fig. 28).

Table 41. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI hyperactivity sub-syndrome

Brain region	Cluster size	p	Coordinates (x, y, z)
Right angular gyrus	136	0.009	38 -48 30

NPI - Neuropsychiatric Inventory

Figure 30. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI Hyperactivity sub-syndrome - 1 significant cluster with peak connectivity in the right angular gyrus



NPI - Neuropsychiatric Inventory

3.3.3.4 Agitation

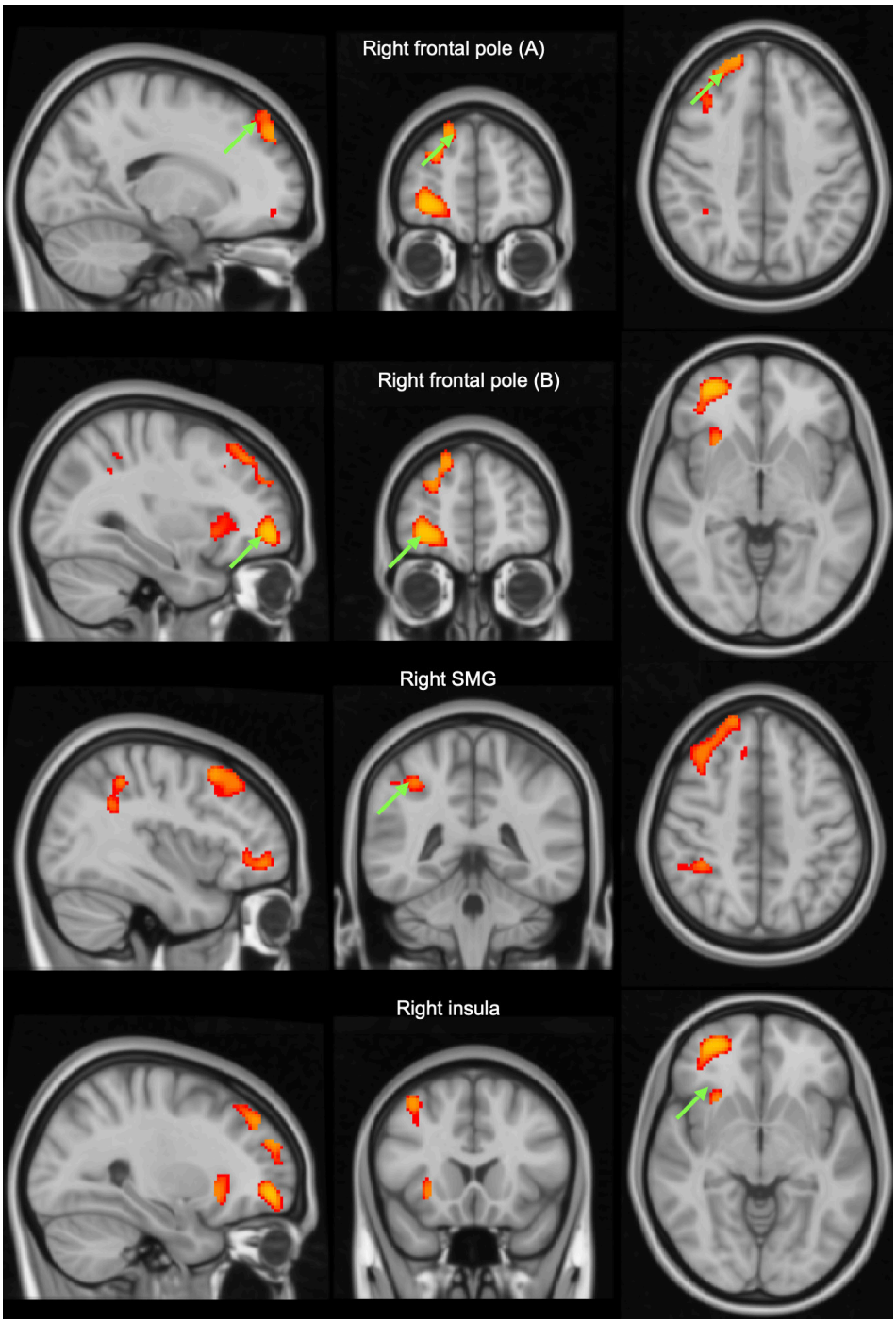
Positive correlation was found between functional connectivity within the right frontoparietal network and total NPI agitation item, with significant clusters of peak connectivity in the right frontal pole, right SMG and right insula. (Table 42, Fig. 29).

Table 42. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI agitation

Brain region	Cluster size	p	Coordinates (x y z)
Right frontal pole (a)	1029	0.021	18 52 40
Right frontal pole (b)	878	0.015	32 52 -4
Right SMG (c)	180	0.027	38 -42 46
Right insula (d)	163	0.025	28 18 -6

NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus

Figure 31. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI agitation



NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus

3.3.3.5 Sleep and night-time behaviour disorder

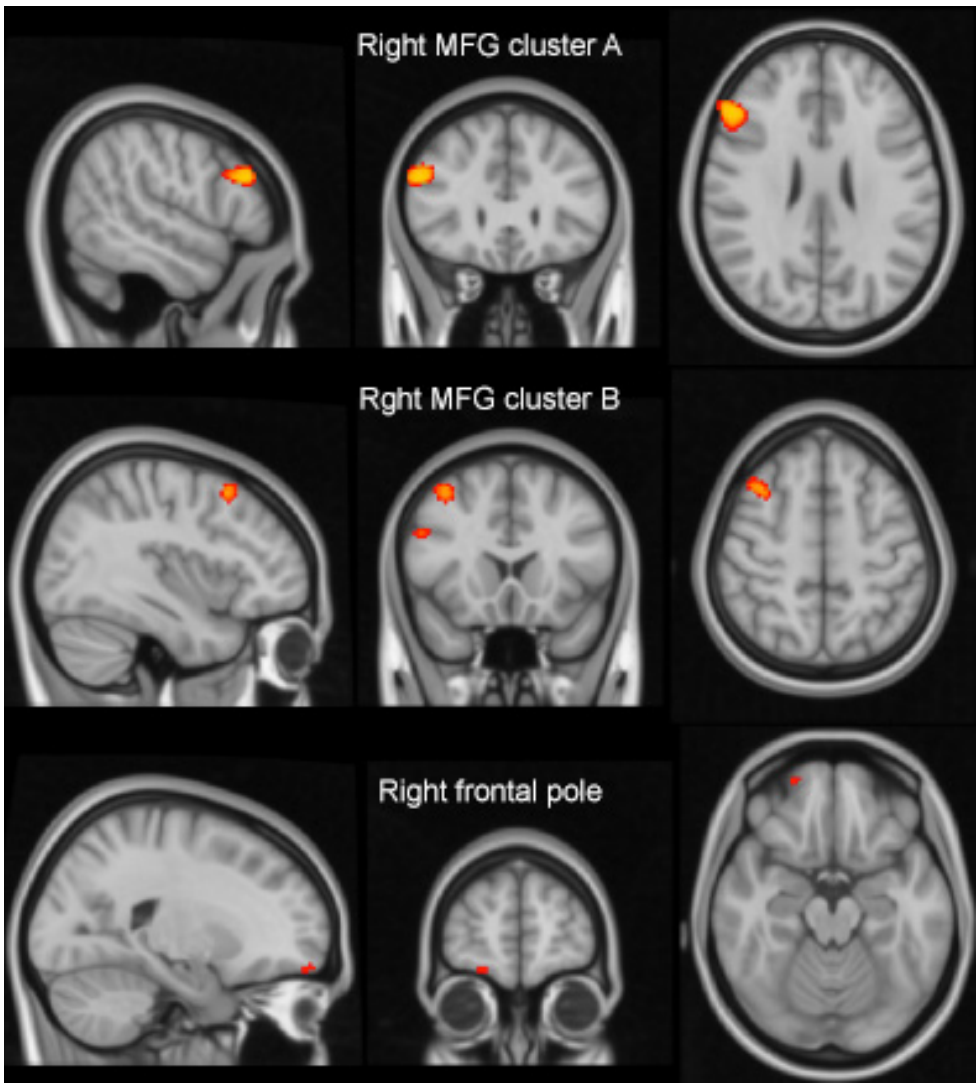
Positive correlation was found between functional connectivity within the right frontoparietal network and NPI sleep and night-time behaviour disorder item, with significant clusters of peak connectivity in the right MFG and right frontal pole (Table 43, Fig. 30).

Table 43. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI sleep

Brain region	Cluster size	p	Coordinates (x y z)
Right MFG (A)	267	0.01	54 28 26
Right MFG (B)	120	0.019	38 18 52
Right frontal pole	17	0.041	22 58 -18

NPI - Neuropsychiatric Inventory, MFG - middle frontal gyrus

Figure 32. Areas of significant correlation between functional connectivity within the right frontoparietal network and NPI sleep and night-time behaviour disorder



NPI - Neuropsychiatric Inventory, MFG - middle frontal gyrus

3.3.4 Connectivity in the left frontoparietal network

We found a positive correlation between connectivity in the left frontoparietal network and NPI scores in NPI Hyperactivity sub-syndrome (Table 44, Fig. 31), as well as in NPI agitation (Table 45, Fig. 32) and NPI irritability (Table 46, Fig. 33) items. There was no statistically significant correlation between functional connectivity in this network and other NPI items or sub-syndromes.

3.3.4.1 Hyperactivity sub-syndrome

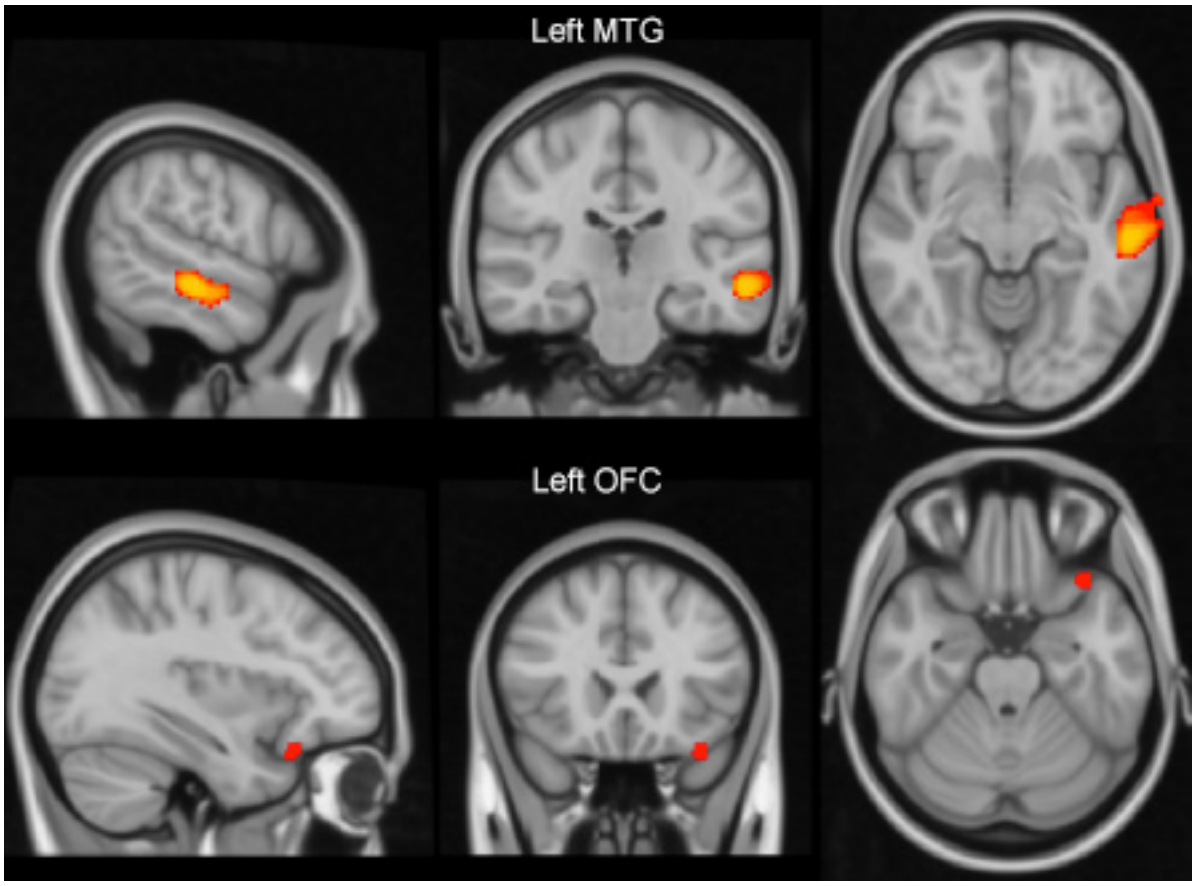
Positive correlation was found between functional connectivity in the left frontoparietal network and NPI Hyperactivity sub-syndrome score with significant clusters of peak connectivity in left middle temporal gyrus, and right and left orbitofrontal cortex (Table 44, Fig. 31).

Table 44. Areas of significant correlation between functional connectivity within the left frontoparietal network and NPI Hyperactivity sub-syndrome

Brain region	Cluster size	p	Coordinates (x y z)
Left MTG	673	0.009	-56 -24 -10
Left OFC	42	0.042	-34 22 -24

NPI - Neuropsychiatric Inventory, MTG - middle temporal gyrus

Figure 33. Areas of significant correlation between functional connectivity within the left frontoparietal network and NPI Hyperactivity sub-syndrome



NPI - Neuropsychiatric Inventory, MTG - middle temporal gyrus, OFC - orbitofrontal cortex

3.3.4.2 Agitation

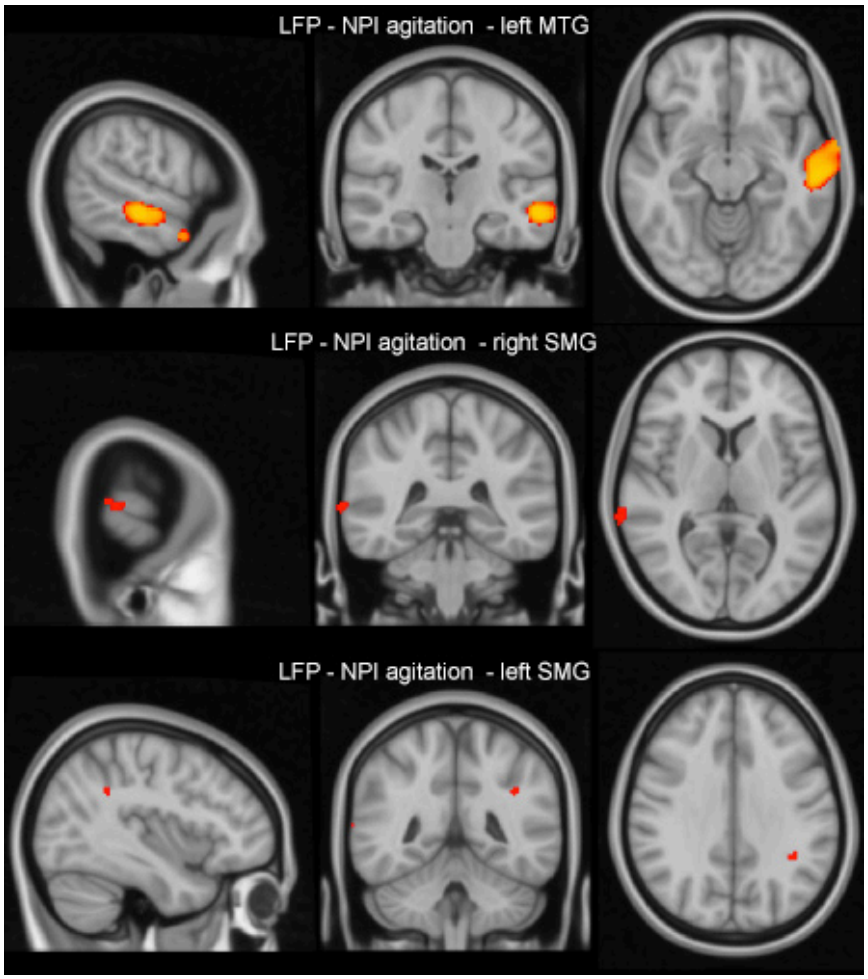
Positive correlation was found between functional connectivity in the left frontoparietal network and NPI agitation with significant clusters of peak connectivity in left MTG, and in the right and left SMG (Table 45, Fig. 32).

Table 45. Areas of significant correlation between functional connectivity within the left frontoparietal network and NPI agitation

Brain region	Cluster size	p	Coordinates (x y z)
Left MTG	965	0.005	-58 -22 -12
Right SMG	51	0.035	70 -38 6
Left SMG	12	0.041	-38 -46 32

NPI - Neuropsychiatric Inventory, MTG - middle temporal gyrus, SMG - supramarginal gyrus

Figure 34. Areas of significant correlation between functional connectivity within the left frontoparietal network and NPI agitation



LFP = left frontoparietal network, NPI - Neuropsychiatric Inventory, MTG - middle temporal gyrus, SMG - supramarginal gyrus

3.3.4.3 Irritability

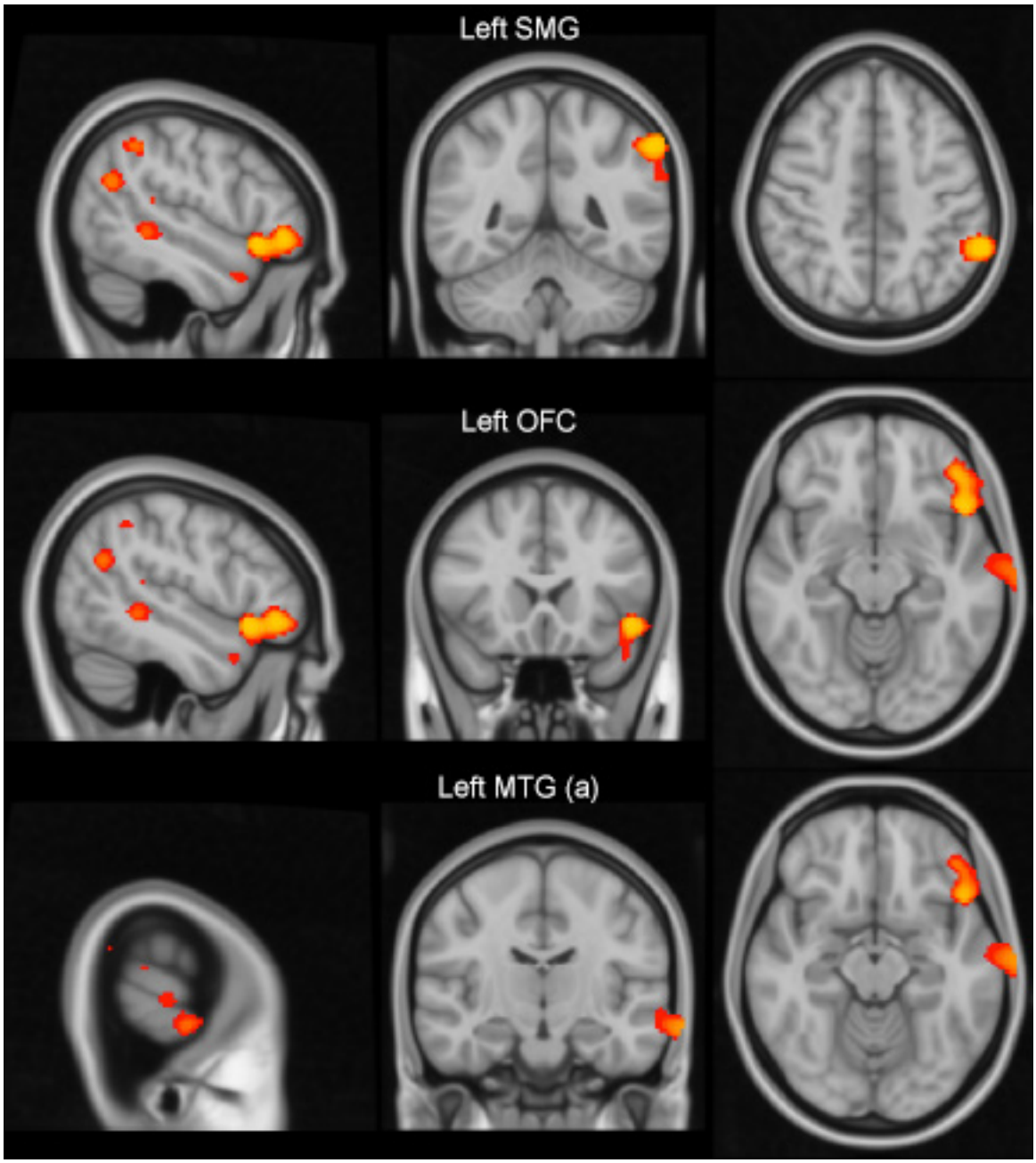
Positive correlation was found between functional connectivity in the left frontoparietal network and NPI irritability score with significant clusters with peak connectivity in left SMG, left OFC, and in 2 clusters in the left MTG (Table 46, Fig. 33).

Table 46. Areas of significant correlation between functional connectivity within the left frontoparietal network and NPI irritability

Brain region	Cluster size	p	Coordinates (x y z)
Left SMG	1167	0.008	-58 -48 46
Left OFC	1028	0.008	-48 20 -12
Left MTG (a)	483	0.017	-76 -14 -16
Left MTG (b)	121	0.027	-50 -42 -4

NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus, OFC - orbitofrontal cortex, MTG - middle temporal gyrus

Figure 35. Areas of significant correlation between functional connectivity within the left frontoparietal network and NPI irritability



LFP - left frontoparietal network, NPI - Neuropsychiatric Inventory, SMG - supramarginal gyrus, OFC - orbitofrontal cortex, MTG - middle temporal gyrus,

3.3.5 Functional connectivity presented by symptom/sub-syndrome of the NPI

This section presents network functional connectivity per symptom or sub-syndrome as measured by the NPI and the networks (and regions) showing positive or negative correlation with the symptom severity. Table 47 lists all the NPI sub-syndromes and items

that were found to be significantly correlated with increased (or decreased in the case of appetite and eating habits) functional connectivity in the four studied resting state networks (Table 47). Only those results that reached significance level of $p < 0.05$ are presented below.

Table 47. Summary of functional connectivity correlation with neuropsychiatric symptoms

Symptom/ sub-syndrome factor	Network	Region	Direction of correlation
NPI total	RFP	R SMG, R frontal pole	Positive
Hyperactivity sub-syndrome	RFP	R angular gyrus	Positive
	LFP	L MTG, L OFC	Positive
Psychosis sub-syndrome	RFP	R MFG, R SMG	Positive
Affective sub-syndrome	SAL	R frontal and parietal operculum, R insula, L IFG	Positive
Anxiety	SAL	L IFG, R insula, R SMG	Positive
Agitation	DMN	R and L precuneus	Positive
	SAL	R SMG, R insula, L frontal operculum, L IFG	Positive
	RFP	R frontal pole, R SMG, R insula	Positive
	LFP	L MTG, R and L SMG,	Positive
Irritability	DMN	R and L PCC	Positive
	LFP	L SMG, L OFC, R and L MTG	Positive

Symptom/ sub-syndrome factor	Network	Region	Direction of correlation
Aberrant motor behaviour	SAL	R insula, R precentral gyrus	Positive
Sleep and Night-time behaviour disorder	DMN	L precuneus	Positive
	RFP	R MFG, R frontal pole	Positive
Appetite and eating habits change	DMN	L precuneus	Negative

NPI - Neuropsychiatric Inventory, RFP - right frontoparietal network, R - right, SMG - supramarginal gyrus, LFP - left frontoparietal network, L - left, MTG - middle temporal gyrus, OFC - orbitofrontal cortex, MFG - middle frontal gyrus, SAL - salience network, IFG - inferior frontal gyrus, DMN - default mode network, PCC - posterior cingulate cortex, ACC - anterior cingulate cortex

3.4 Summary of results

Chapter 3 presented findings from the analysis of clinical and imaging data. We have not found significant correlation or group differences relating to change in performance on ADL. We have found that regional atrophy was associated with neuropsychiatric symptoms measured at 3-year follow-up, including in less studied brain regions such as the cerebellum. Functional connectivity analysis showed correlation between increased connectivity within the four studied networks and some of the neuropsychiatric symptoms. Agitation appears to be associated with increased connectivity in multiple regions. The findings are further discussed in the next chapter.

CHAPTER 4. DISCUSSION

This chapter will discuss the key findings in this PhD project. It will present strengths and weaknesses, and outline implications for practice and future research recommendations.

4.1 Clinical data

4.1.1 Demographic data and the population-representativeness

Our study was designed to apply quantitative MRI techniques in a 'real-life', clinical population of people attending a community-based memory clinic for an assessment of their cognitive complaints. This real-life setting is reflected in the relatively old age of the study sample, as well as evidence of co-morbid disorders and the presence of other brain pathologies, such as small vessel disease. One of the advantages of performing a brain imaging analysis in such a population is that it potentially increases the generalisability of the results. Previously, even large-sample imaging studies, such as those based on ADNI databases, have been criticised for their relatively 'selective' recruitment, often originating from specialist (and selective) neurology centres and are therefore not fully comparable to community-based samples (Gianattasio et al., 2021). Studies comparing cohorts on ADNI register against population-derived samples show differences in imaging biomarkers, such as hippocampal volume and the rate of hippocampal atrophy (Whitwell et al., 2012).

The patient cohort in this study was relatively, but not fully, representative of the population of West Sussex seeking memory assessment. The clinical pathway for diagnosing cognitive disorders in the local area involves a referral to a memory assessment service (MAS), from which the study sample derives. However, not all patients referred to memory clinic required brain imaging in the form of an MRI scan during the assessment. Some patients would have had a relatively recent CT or MRI scan on referral, in which case the clinical pathway relied on the existing imaging in the diagnostic process. Additionally, some patients, due to age, fragility, and their comorbidities (such as those that may prevent, or make uncomfortable having an MRI scan), or advanced cognitive dysfunction, were referred for a CT scan. Finally, some patients would have chosen to have an MRI scan performed in a local hospital, or declined to take part in this study due to the extended scanning time as compared to a clinical one. There are no data on the MAS population

as a whole to compare with but it is likely that the study cohort was younger (mean age 76.7 years), less cognitively impaired (48 participants had a non-dementia diagnosis at baseline, with mean ACE-R score of 82/100), less physically fragile, and more likely to have support from family and friends (e.g. transport to the scanning centre) when compared to the general MAS population in this area. Nevertheless, they are more likely to reflect general MAS population as compared to patients who attend assessment in specialist centres.

The overwhelming majority of the clinical sample were of white British ethnicity (94%). This is generally representative of the population in West Sussex, where 89% of population identifies as White British (ONS, 2011), with an even lower proportion in older age groups such as the MAS population. However, given that people from minority ethnic groups may have a higher prevalence of cognitive impairment driven by factors such as cardiovascular disease for the black Caribbean population (Mathur et al., 2011, Brothers et al., 2019) and diabetes for south Asians (Jones et al., 2020), people from minority ethnic groups may be underrepresented in this sample. This may be related to the ways services are set up with little specific outreach into minority ethnic groups. In West Sussex, there are regional variations in ethnicity - Crawley has a higher percentage of ethnic groups who are not classified as White British, reaching nearly 28% (ONS, 2011). Crawley also has some of the higher rates of social deprivation (MHCLG, 2019), which might have influenced access to transport and the ability of patients to get to a scanning department used for the study, which was situated outside the local health infrastructure. It has been reported that both ethnicity and social deprivation have an impact on access to a timely dementia diagnosis, although the former does not always influence the threshold for referral to memory service (Wilson et al., 2020).

The majority of the sample at baseline had a non-dementia diagnosis of aMCI or SCD - this is a reflection of the pragmatic assessment pathway in this memory clinic, where less impaired patients were considered to require an MRI rather than a CT in the course of their diagnostic process. Additionally, people who were less cognitively or functionally impaired were potentially more receptive to the prospect of a longer scanning time (about 8 minutes longer as compared to the non-research, clinical MRI scan).

We found no statistically significant differences in age, gender and ethnicity between the group of people recruited to the study and those who were invited to participate but declined or did not respond to the invitation. This suggests that no particular bias relating to demographic factors had been introduced at the stage of study recruitment. However the sample size is small and therefore the statistical power to identify such variation is limited.

There was a statistically significant age difference between people with dementia and those with non-dementia diagnosis. Considering that age is a significant risk factor for all cause dementia, including AD, it may have contributed to the clinical presentation and therefore influenced the diagnostic category (Livingston et al., 2017).

4.1.2 Place of residence

At baseline, all participants lived at home, alone or with family members, but this situation changed at 3-year follow up, when 5 participants lived in a care home and some of those living at home without other family members had a live-in carer, due to care needs consistent with the progression in cognitive and functional impairment. All of the participants who moved to a care home or had a live-in carer met the criteria for a diagnosis of dementia at the time of follow-up. The majority of participants with dementia still lived at home (n=41), which reflects the relatively mild severity of dementia in this cohort.

4.1.3 Education

The study participants were on the whole well educated, with the mean age of leaving full-time education of 17 for both men and women. In our study, there was no statistically significant difference in education between people with AD vs. non-AD diagnosis at follow-up. Low education level is considered a risk factor for dementia (Livingston et al., 2017, Livingston et al., 2020). In our sample, accounting for the typical age of children starting school at the age of 5 (Butler, 1944), the average time spent in full-time education was 11 years. In the literature, the thresholds between high and low levels of education vary between sources, usually between 6 and 9 years (Meng and D'Arcy, 2012), which would

place the average education background of the study cohort at a relatively high level.

The ‘neuroprotective’ mechanism of educational attainment is not clearly elucidated but is likely to be a function of cognitive reserve (Livingston et al., 2017). A recent paper reported that older people with college degree education had better organisation of resting state brain networks over the follow up of 3 years, including higher degree of between-network separation and lower within-network correlation. Decline in between-network separation has been observed to be predictive of worsening in dementia severity (Chan et al., 2021).

4.1.4 Cognitive performance and diagnosis

The majority of participants (n=50, 63.3%) had a non-dementia diagnosis at baseline. The change in cognitive scores in this cohort is relatively modest, which reflects the fact that just over a half of participants in this group of the cohort remained at the non-dementia status at follow up (n=26, 52% of the baseline non-dementia group). Twenty-four of baseline 'non-dementia' participants met the clinical criteria for dementia at follow up, which translates into a 3-year conversion rate of 48%. The expected rate of ‘conversion’ from MCI to Alzheimer’s disease varies and depends on a number of characteristics - an annual conversion rate in a community outreach sample can be as low as 3%, compared with 13% in a group recruited through memory clinic (Farias et al., 2009, Mitchell and Shiri-Feshki, 2009). This annual conversion rate may be considerably higher - around 30% - in selected populations such as those with amnestic MCI (Schmidtke and Hermeneit, 2008) or in clinical samples with high levels of amyloid positivity (Ottoy et al., 2019). The conversion rate in our sample falls in between the latter two values, which reflects the application of clinical diagnostic criteria in the absence of biomarker confirmation. It is possible that if only amyloid-positive participants with MCI or SCD were recruited into the study, the conversion rate would have been higher. The rates of progression from SCD to dementia are lower, most likely due to heterogeneity inherent in the current SCD concept. The reported annual rates of progression from subjective memory complaints to dementia is 2.3% and to MCI 6.6 % (Mitchell et al., 2014). In our cohort, 8 participants had SCD at baseline, one of whom met the criteria for aMCI at follow-up. Because of the small number, it is difficult to draw conclusions about the conversion rate in this diagnostic category.

In our study, there was a statistically significant difference in cognitive performance at baseline between people who had AD vs non-AD diagnosis at follow-up. This was specifically seen in total ACE-R and MMSE scores as well as in sub-scores in memory and visuospatial skills domains, which are considered to be sensitive for identifying cognitive deficits at early stages of AD (Mandal et al., 2012, Aggleton et al., 2016).

4.1.5 Activities of daily living

Performance in daily living activities was measured using BADLS, completed by the study partners. As with cognitive performance, the BADLS scores reflect a high level of daily functioning in the study group, with nearly half of the cohort showing no functional impairment at baseline. This is consistent with the distribution of diagnostic categories at baseline (most participants had no evidence of dementia). There was a statistically significant difference in total BADLS score as well as sub-scores on factors of instrumental activities of daily living and orientation at baseline when comparing the AD and non-AD groups (diagnosis at follow-up). As expected, at 3 year follow up, the proportion of participants with functional impairment increased as reflected by the mean and median scores on the whole BADLS scale as well as its four factors, with the highest median increase in the factor of instrumental daily living activities and orientation items.

4.1.6 Risk factors and comorbidities

The relatively advanced age of study participants may partially explain the high prevalence of cardiovascular risk factors in this cohort, with the majority (n=59, 74.7%) having at least one comorbid illness. Most common was hypertension, recorded in the medical history of nearly half of participants (N=39, 49.4%). The importance of modifiable vascular risk factors in the pathogenesis of Alzheimer's disease has been established previously, with mid-life hypertension emerging as an important target for preventative interventions to lower the prevalence of dementia (McGrath et al., 2017, Abell et al., 2018, Livingston et al., 2020). A few brain imaging studies found that a degree of grey matter volume loss in cortical areas such as the posterior cingulate cortex or the hippocampus may be influenced by the presence of vascular risk factors such as hypertension (de la Torre, 2018, Suzuki et al., 2019, Lamar et al., 2020).

In our cohort, the prevalence of cardiovascular risk factors was not statistically significantly different between the AD and non-AD groups.

4.1.7 Clinical brain imaging findings

The study participants had their MRI scans performed in the course of their diagnostic assessment. As such, all scans were read and reported by a consultant neuroradiologist with expertise in the imaging of cognitive disorders. The clinical reports included qualitative findings, such as the presence of brain atrophy, evidence and severity of cerebrovascular disease as well as the presence of microhaemorrhages. The most common finding was the presence of small vessel disease, which was reported in three quarters of the total study cohort, though it was of predominantly mild severity. Participant age was positively correlated with the presence of small vessel disease of any severity.

Small vessel disease and other microvascular changes, considered together as white matter hyperintensities (WMH), are highly prevalent in the older population (Grueter and Schulz, 2012). In older people with dementia, where 'pure' AD pathology may be present in just over 20% of cases, white matter lesions can be found in over 90% of study populations (Fernando and Ince, 2004). High volume of WMH appears to be associated with an AD-like pattern of brain atrophy as compared to an age-related pattern of atrophy, which may indicate that vascular burden increases the risk of neurodegeneration, especially when combined with vascular risk factors (Habes et al., 2016).

4.1.8 Hippocampal atrophy

Hippocampal atrophy is considered to be one of the biomarkers reflecting neurodegeneration in AD (Gosche et al., 2002, Jack et al., 2002, Jack et al., 2011, Pini et al., 2016) and as such is considered as evidence of pathological process in the diagnostic criteria for dementia due to AD (McKhann et al., 2011). A recently proposed diagnostic framework, based on the presence of biomarkers of beta-amyloid deposition, pathological-tau and neurodegeneration [A/T(N)], rather than a syndromal construct of AD, lists atrophy on MRI as a marker of neurodegeneration or neuronal injury [N in the A/T(N) framework] (Jack et al., 2018). Less than a quarter of our participants had hippocampal atrophy reported at their baseline MRI.

This may appear low, considering that 30 participants (37.9%) met the criteria for AD at the time of the baseline MRI scan, and that number rose to 53 (67.0%) at the follow-up. However, whilst hippocampal atrophy is considered to be the one of the most consistent and reliable markers of neurodegeneration in AD, this finding is based on studies using quantitative, and increasingly semi-automated, methods of measuring brain volume (Jack et al., 2011, Uysal and Ozturk, 2020), which is not currently the clinical practice in the NHS. The qualitative assessment of an MRI for the purpose of clinical reporting may not detect early regional atrophy in a sample of relatively mildly affected participants. Moreover, a recent Cochrane review showed that using the MRI-derived volume of hippocampus and medial temporal lobe had low sensitivity and specificity as a stand-alone test for early diagnosis of Alzheimer's disease in people with MCI (Lombardi et al., 2020).

Additionally, whilst hippocampal atrophy has been linked to other neurodegenerative processes such as hippocampal sclerosis or primary age-related tauopathy, it can also be influenced by the presence of other proteinopathies such as TDP-43 (Josephs et al., 2020). In an earlier study, Josephs and colleagues found that presence of TDP-43 in the hippocampal regions was associated with faster rate of hippocampal atrophy when compared to AD participants who had no TDP-43 presence and those where it was limited to amygdala. The study included over 800 participants with neuropathology confirmed at autopsy, but the participants were older when compared to this study cohort, which increased the risk of multiple brain pathologies and overlap syndromes, it is therefore difficult to extrapolate the findings to younger people with AD. Another study suggested that ventricular volume trajectory may be a more sensitive marker of AD progression than total brain or hippocampal atrophy However, this cohort also included participants who were older, and whilst it controlled for the presence of cerebrovascular disease and Lewy body pathology, it did not consider other pathological factors, such as TDP-43 (Erten-Lyons et al., 2013).

Risacher and colleagues used volumetric MRI to classify participants into three distinct groups based on the pattern of cortical atrophy, based on the ratio of hippocampal to global cortical volume: hippocampal-sparing, limbic-predominant and typical AD. The clinical features of participants with various cortical atrophy patterns were similar at baseline, with only the hippocampal sparing group showing more executive dysfunction.

This suggests that clinical presentation consistent with aMCI may be associated with different cortical atrophy patters, not necessarily showing preferential regional atrophy in the hippocampus (Risacher et al., 2017). The limitation of this study was that it only included participants with dementia and not those with preclinical AD, such as MCI or SCD. Additionally, as in the majority of ADNI studies, with participants recruited from specialist centres, it may not be generalisable to population of community-based patients with AD dementia.

4.1.9 Neuropsychiatric symptoms

In our study, participants were assessed with NPI at the time of their 3-year follow-up. This does not allow for a comparison with the baseline status, but it enables us to test the hypothesis about the value of brain imaging in predicting neuropsychiatric symptoms.

Our results show that the most common neuropsychiatric symptom in the whole cohort was irritability, reported by 48.0% of the participants, followed by depression in 44.0%. Agitation, anxiety, apathy and changes in appetite and eating habits were reported by just over a third of study group (36.0%). The NPI items reported by a relatively low number of participants - or specifically their study partners - included elation (only one participant), as well as hallucinations (0.8%), disinhibition (17.3%) and delusions (18.7%). The majority of our participants had a relatively mild degree of cognitive impairment, so this appears consistent with a recent review paper that found elation, disinhibition and psychotic symptoms to be infrequent at the MCI stage (Martin and Velayudhan, 2020).

There were differences between AD and non-AD groups in the severity of some, but not all NPI items - for example, the severity of the total NPS burden, the Hyperactivity and Apathy sub-syndromes, as well as the single items of delusions, agitation, apathy and appetite and eating habits was higher in the AD group. These finding are consistent with the previously reported trajectory of neuropsychiatric symptoms burden in the course of AD, where the severity of some symptoms in general may periodically increase in the moderate and severe stage (Lyketsos et al., 2002, Wadsworth et al., 2012, Spalletta et al., 2015).

Apathy is a recognised and common symptom in MCI (Gallagher et al., 2017), and in cognitively unimpaired older adults (Creese et al., 2020), but it also has a high persistence and incidence throughout the course of dementia (van der Linde et al., 2016). In our study the prevalence of apathy was higher in the AD group. Previously, apathy was found to increase the risk of progression from MCI to dementia, though there are conflicting reports in the literature (Martin and Velayudhan, 2020). In our cohort, participants in the non-AD group remained cognitively and functionally stable over the 3-year follow-up and therefore may generally have a lower risk of progression to dementia, considering that this risk appears higher in the first 18-24 months following the MCI diagnosis (Busse et al., 2006).

There were no differences between AD and non-AD in the severity of the Psychosis and Affective sub-syndromes, or in single NPI items of depression and anxiety. This is consistent with the reported prevalence of neuropsychiatric symptoms in early AD, including mild dementia and MCI stages. NPS may occur in 35-85% of people with MCI and may even precede the onset of cognitive impairment (Hallikainen et al., 2012, Gallagher et al., 2017, Martin and Velayudhan, 2020). Previously, it has been reported that particular neuropsychiatric symptoms, such as apathy and anxiety, can increase the odds of progression from MCI stage to dementia, but a recent review found that the evidence is still conflicting for symptoms such as depression or sleep problems (Martin and Velayudhan, 2020)

4.2 Voxel Based Morphometry

4.2.1 Correlation between grey matter volume and activities of daily living

Our study set out to explore whether brain imaging can provide prognostic information about the trajectory of AD in an individual, and specifically the risk of a more rapid functional decline and the probability of developing neuropsychiatric symptoms.

In our results, we did not find any correlation between the regional GM volume and ADL as measured by the total BADLS score or when analysing the BADLS factors of IADL, self-care, orientation, or mobility at 3 year follow-up. There have been a number of studies that found an association between regional brain volume and ADL. Mioshi and colleagues

studied neural correlates of ADL in AD and FTD and found a correlation between ADL scores and widespread atrophy in temporal, frontal, and parietal cortex as well as caudate nucleus. This study had a cross-sectional design, where participants' brain imaging was performed at the time when they had established symptoms of dementia, and according to the mean cognitive scores reported in the paper, were more impaired, both functionally and cognitively, as compared to our study sample (Mioshi et al., 2013). Our study was designed to test the value of neuroimaging in predicting the level of functional decline in the future and the participants had a relatively low level of functional impairment, if any, at the time their brain imaging was performed. The instrument used by the Mioshi and colleagues differed from BADLS, and was possibly more sensitive. Slachevsky and colleagues found an association between regional brain volume and sub-types of ADL, measured with a different instrument in a cross-sectional study of 63 participants including both people with AD and healthy controls (Slachevsky et al., 2019). Jutten and colleagues found a correlation between instrumental ADL and GM volume in medial temporal lobes, precuneus and cingulate cortex (Jutten et al., 2019). Both studies were performed using a cross-sectional design and included participants with more advanced impairment, therefore were more likely to find the correlation between regional cortical volume loss and clinical measures. In contrast, Borda and colleagues did not find a correlation between hippocampal subfield volumes and ADL in people with AD or DLB (Borda et al., 2020). Nadkarni and colleagues found a correlation between measures of IADL and brain perfusion, in a study of participants with AD and healthy controls - however, the difference of techniques between that study and ours does not allow for direct comparison (Nadkarni et al., 2012). Marshall and colleagues studied both cross-sectional and longitudinal relationship between cortical thickness and IADL - that study found significant correlation between cortical thickness in temporal areas and baseline and longitudinal IADL and in parietal regions and longitudinal IADLs. The authors used a potentially more sensitive ADL tool and a larger study sample, which could have made detecting the correlation easier (Marshall et al., 2014). In our sample, the BADLS scores, particularly at baseline, but to some degree also at follow-up, was relatively narrow (mean of 12.7 and median of 9.0 of total BADLS score at follow-up), due to mild ADL impairment of participants. This could have contributed to the negative finding of lack of correlation between regional volume changes and the ADL measures. Whilst this negative result is consistent across all BADLS measures, it is possible that a correlation between ADL measures and regional

brain volume could be found in a bigger sample, or one that is more diverse in terms of functional status, i.e. including a larger number of participants with moderate and severe ADL impairment. Finally, BADLS score is subjective to some degree, as it depends on carer report and may have therefore affected the strength of correlation - using more objective measures or participant functional performance, such as Assessment of Motor and Process skills (Bray et al., 2001), or using wearable technology, could have potentially reduced the subjective reporting bias.

4.2.2 Correlation between grey matter volume at baseline and neuropsychiatric symptoms at follow-up

Our results show significant negative correlation between regional brain volume and selected NPI measures within the AD group (n=52), but not in the non-AD group.

A review of neuropsychiatric symptoms in AD and their neural correlates found multiple regions associated with various symptoms or syndromes, and the results were sometimes conflicting (Rosenberg et al., 2015). This may be due to an overlap between neuropsychiatric symptoms and the heterogeneity between studies. Another approach, adopted by Tascone and colleagues, involved grouping people with AD into two categories: with a high or low number of neuropsychiatric symptoms - their study showed distinct patterns of regional brain atrophy between participants with a high vs. low number of neuropsychiatric symptoms when compared to healthy controls (Tascone et al., 2017).

In the group of participants with AD diagnosis at follow-up, the total NPI score, reflecting the global burden of neuropsychiatric symptoms, was negatively correlated with the grey matter volume in the left orbitofrontal cortex and the posterior cerebellum (crus I and II) bilaterally. The orbitofrontal cortex has been considered previously as potentially linked to an increased risk of neuropsychiatric symptoms, most frequently implicated in apathy (Donovan et al., 2014b, Rosenberg et al., 2015). Nakaaki and colleagues linked atrophy in the right orbitofrontal cortex, as well as the inferior frontal cortex and several other areas to the increased risk of developing delusions in the course of AD (Nakaaki et al., 2013). Whitehead and colleagues also found reduced cortical thickness in the left medial orbitofrontal cortex and in the left superior temporal region in female participants

with AD and paranoid delusions (Whitehead et al., 2012). In our study, a relatively small number of participants developed delusions or hallucinations, which makes it difficult to look for neural correlates of those single NPI items, especially as the latter appear to have distinct types (e.g. paranoid or misidentification type) and therefore may have different neuropathological basis (Reeves et al., 2012). In our AD group, the Psychosis sub-syndrome, which includes NPI items of delusions, hallucinations and sleep and night-time behaviour disorder, was inversely correlated with the regional brain volume in the right inferior frontal lobe (frontal operculum area). The frontal cortex has been implicated in previous studies showing volumetric differences as well as reduced perfusion and metabolism in the prefrontal cortex in patient with AD and delusions (Reeves et al., 2012).

NPI Psychosis sub-syndrome in our study showed an inverse correlation with the GM volume in the region of the right frontal region of operculum, inferior frontal gyrus and the insula. This appears consistent with previous reports of a reduced GM volume in the right insula in correlation with psychosis or hallucinations in AD as well as reduced glucose metabolism in the right frontal areas (Blanc et al., 2014, D'Antonio et al., 2019). Pathology in the insula, with its role in processing emotions and sensory stimuli such as interoception (Critchley et al., 2004) and connections to the limbic system and various cortical areas, is an often reported finding in studies of schizophrenia (Wylie and Tregellas, 2010). Smaller volume and cortical thickness in the insula were also reported in a large cohort of adults with a psychotic disorder as well as adolescents on the psychosis spectrum (Sheffield et al., 2021). Additionally, the insula is overactive in pathological anxiety and forms a network with ACC and mPFC that detects and responds to internal signals (Robinson et al., 2019).

4.2.3 The neocerebellum as a region of interest in neuropsychiatric symptoms associated with Alzheimer's disease

We found a significant inverse correlation between the total NPI score and the grey matter volume in the posterior cerebellum (crus I and II). Whilst cerebellar atrophy has not been a strong focus of research in dementia disorders, and previous studies showed its relative sparing in AD-related brain atrophy (Karas et al., 2003), more recent projects demonstrated identifiable and disease-specific patterns of cerebellar volume loss in various neurodegenerative conditions, including AD (Guo et al., 2016a, Gellersen et

al., 2017). Posterior regions of cerebellar hemispheres, such as crus I and II have been demonstrated to play a role in non-motor processes, including social cognition and mentalising (Van Overwalle et al., 2020) and through cerebral-cerebellar loops in complex behavioural, emotional and cognitive functioning (Schmahmann, 2001, Buckner, 2013).

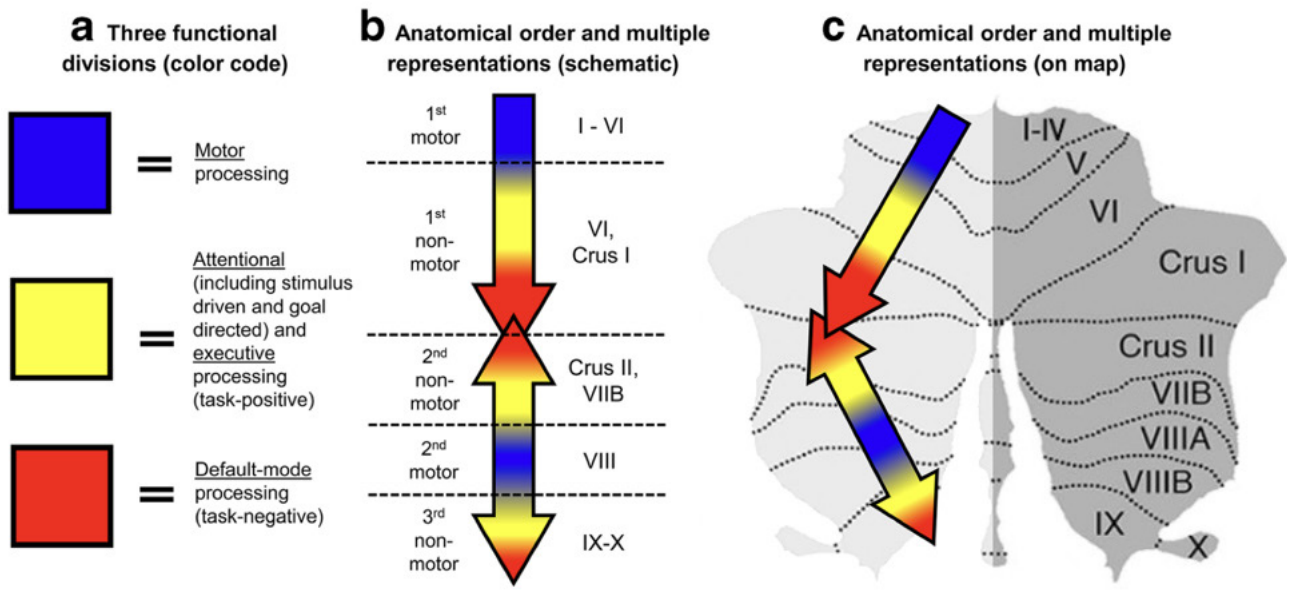
Guo and colleagues found a correlation between cortical and cerebellar atrophy in crus I and II area in Alzheimer's disease, which was different in pattern from that observed in bv-FTD (Guo et al., 2016a). Reduced volume in the posterior cerebellum, including the crus I area was found in subjects with AD but not MCI or in healthy controls (Toniolo et al., 2018). Whilst atrophy in crus I and II areas appears to be linked predominantly to AD, other authors reported this finding in people with other neurodegenerative disorders, such as DLB and a proportion of subjects with FTD linked to C9orf72 mutation (Colloby et al., 2014, Bocchetta et al., 2021).

In a meta-analysis that compared age-related cerebellar atrophy with one observed in the AD, the effects of ageing appeared to affect bilateral regions of posterior cerebellum such as crus I/II and lobule VI, but a strict lateralisation to the right was observed in AD group (Gellersen et al., 2021). In our study, the severity of Psychosis sub-syndrome showed right lateralisation, whereas total NPI score as well as the severity of sleep and night-time behaviours item was correlated with atrophy in crus I and II bilaterally.

The cerebellum is now recognised as a structure involved in regulating almost all aspects of behaviour (Schmahmann et al., 2019). Several areas of the neocerebellum have been linked to resting state networks in a study by Habas and colleagues (Habas et al., 2009). Crus I and II were in particular connected to left and right executive control network, also known as frontoparietal network, whilst lobule VI contributed to the salience network and lobule IX to the default mode network (Habas et al., 2009). Our resting state fMRI data analysis showed increased connectivity in areas of right frontoparietal network in correlation with overall NPI score and the severity of the Psychosis sub-syndrome, which were also negatively correlated with the grey matter volume in the posterior cerebellum. The role of the posterior cerebellum in mediating emotional and behavioural responses has been discussed by Guell and Schmahmann (Guell and Schmahmann, 2020). In an earlier paper, the authors described 3 fundamental poles of cerebellar function: motor, attentional/executive, and default-mode (Fig. 36) (Guell et al., 2018). A syndrome of

cognitive and behavioural changes related to cerebellar pathology, predominantly in the posterior lobe and/or the vermis, was characterised and conceptualised as the cerebellar affective cognitive syndrome, involving deficits in executive function, visuospatial skills, language processing and emotion regulation (Schmahmann and Sherman, 1998, Argyropoulos et al., 2020).

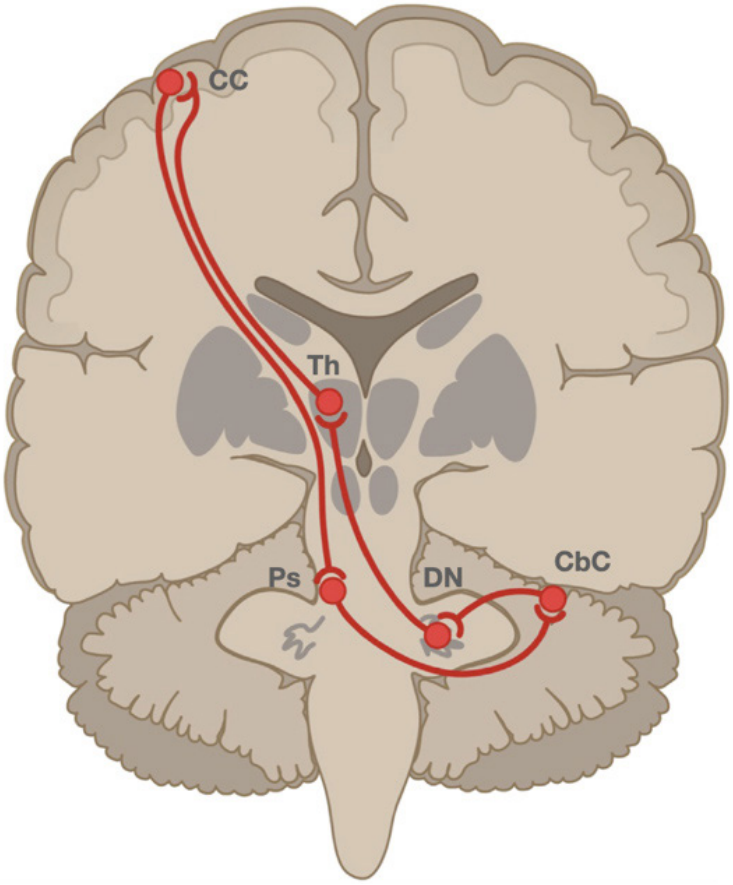
Figure 36. Three fundamental poles of cerebellar function and anatomical representation, adapted from Guell and Schmahmann, 2020 (Guell and Schmahmann, 2020)



The cerebellum appears to be organised topographically in regions involved predominantly in motor control circuits (anterior lobe and parts of lobule VIII), cognitive function (lobule VI VII, VIIb, crus I and II) and emotional and social behaviour. Cerebellar-cortical-limbic circuits (Fig. 37), involving the posterior vermis could contribute to neuropsychiatric symptoms in case of its dysfunction (Stoodley and Schmahmann, 2010, Villanueva, 2012). A more recent study found altered connectivity between dentate nucleus and cerebral cortex in bipolar affective disorder (Olivito et al., 2021). Cerebellar atrophy has been previously reported in people with schizophrenia, very late onset schizophrenia-like disorder and in first degree relatives of people with schizophrenia (Okugawa et al., 2002, Konarski et al., 2005). Other conditions that have been linked with alteration in the structure and connectivity of the cerebellum include depression (Depping et al., 2018). A neurodegenerative cerebellar ataxia is often associated with neuropsychiatric symptoms,

with as many as 95% of people affected by the condition reporting at least one symptom in the NPI-Q questionnaire, most commonly anxiety, depression, sleep and night-time behaviour change, irritability, disinhibition, agitation and changes in appetite (Kronemer et al., 2021).

Figure 37. Cerebro-cerebellar circuit adapted from Buckner, 2013 (Buckner, 2013)



CC - cerebral cortex, Th - thalamus, Ps - pons, DN - dentate nucleus, CbC - cerebellar cortex

In our study, NPI Psychosis sub-syndrome was inversely correlated with the regional volume in the right crus I and II. Previously separate case studies reported a new onset psychosis following cerebellar strokes (Bielawski and Bondurant, 2015, Neufeld et al., 2016, Liao et al., 2018) or a cerebellar tumour (Nkire et al., 2011), in addition to the body of evidence implicating alterations in cerebellar structure and connectivity with schizophrenia (Moberget and Ivry, 2019). Whilst in our sample a relatively low number of participants reported hallucinations and delusions, the severity of the Psychosis factor

could have been influenced by the contribution from ‘sleep and night-time behaviours’ item, which independently was also found to be inversely correlated with the grey matter volume in crus I bilaterally.

Our findings add to the body of evidence that the neocerebellum, and particularly areas of crus I and crus II, is involved structurally and functionally in AD. The posterior cerebellum has also been postulated to contribute to functional connectivity within the DMN as well as frontoparietal networks. Our study showed a negative correlation between regional brain volume in the posterior cerebellum and the total NPI score as well as the score in the NPI Psychosis factor and sleep and night-time behaviour disorder item, all of which, as will be discussed further, were associated with an increased connectivity frontoparietal network (sleep was also associated with increased connectivity in DMN).

4.2.4 Structural neural correlates of sleep and night-time behaviour disorder and anxiety items of the neuropsychiatric inventory

Our volumetric analysis showed inverse correlation between grey matter volume in the right crus I region and the severity of sleep and night-time behaviour item of the NPI. Whilst disordered sleep is a well-documented feature of AD, there is a limited number of studies on its neural correlates. A reduction in GM volume in the precuneus region in subjects with AD who scored 1 and above in the sleep item of the NPI as compared with participants without sleep disorder was previously reported (Matsuoka et al., 2018). In a recent VBM case-controlled study of subjects with insomnia, the researchers found an increased GM volume in the right crus II area (Li et al., 2021b). Brain perfusion studies have shown evidence of reduced a rCBF in inferior frontal gyrus and temporal pole bilaterally, right precentral gyrus as well as an increased rCBF in the right precuneus, right occipital pole and left middle occipital gyrus in participants with AD and sleep disturbance (Im et al., 2017). In our connectivity analysis, we found significant positive correlation in the bilateral precuneus connectivity within the DMN and the severity of sleep and night-time behaviour item of the NPI - these finding could indicate a compensatory functional activation in this region.

Our results show an inverse correlation between the anxiety item of the NPI and regional GM volume in the left posterior and anterior cingulate as well as the right superior parietal

lobule, extending medially to precuneus. This is consistent with previously reported neural correlates of anxiety in AD in the literature, such as a reduced GM volume in the left posterior cingulate (Mohamed Nour et al., 2021), and in the right precuneus and inferior parietal lobule, in combination with an increased perfusion in the ACC bilaterally (Tagai et al., 2014). Atrophy in ACC was previously reported in association with severity of agitation as measured by NPI (Bruen et al., 2008) in subjects with AD.

Dorsal ACC is also a part of salience network - our study revealed positive correlation between the connectivity within the salience network and Affective sub-syndrome as well as anxiety, agitation and aberrant motor behaviour items of the NPI.

The links between anxiety and structural or functional alteration in the precuneus have been reported before - meta analysis of imaging studies in social anxiety disorder showed an increase in GM volume in the left precuneus in adults with social anxiety group as compared to healthy controls. There have also been differences in the same direction reported in the frontal, temporal and parietal cortices (Wang et al., 2018). A positive correlation between GM volume in middle temporal gyrus, operculum, middle cingulate and precuneus and anxiety measures in subjects with relatively mild anxiety was reported in a study by Besteher and colleagues (Besteher et al., 2017).

4.2.5 A summary of findings from voxel-based morphometry

Our study suggests that regional grey matter volume loss is associated with, and potentially predictive of, the severity of neuropsychiatric symptoms as measured by total NPI, Psychosis sub-syndrome as well as sleep and anxiety items at 3 year follow-up. Our approach is unique in that the MRI correlates precede the measurement of our clinical variables by 3 years, unlike the previously published reports. While we cannot definitively conclude those imaging finding are directly predictive of neuropsychiatric status at 3 year follow-up, those associations are statistically significant and should encourage further studies of their prognostic value. The brain regions implicated in our analysis, such as prefrontal and cingulate cortex, have previously been linked to neuropsychiatric symptoms in AD and in other psychiatric disorders in younger people. Neocerebellar regions of crus I and II have not been a major focus of study in the field of AD and dementia in

general, however, our findings suggest that cerebellar atrophy may be associated not just with cognitive dysfunction in dementia, or psychiatric disorders in general, but also with neuropsychiatric symptoms in AD, which may have a different neurobiological basis

4.3 Connectivity

4.3.1 Connectivity analysis in correlation with daily living activities

In our study, we have found a correlation between the connectivity within resting state networks and the severity of neuropsychiatric symptoms after 3 years, but not with the impairment in daily living activities at baseline, follow-up or change between the two time points. Other authors have found associations of selective, mobility-related ADL features such as a reduced life-space mobility with disrupted connectivity between DMN and sensorimotor network (Hsu et al., 2020). Altered inter-network connectivity between frontoparietal and sensorimotor networks was also reported in participants with MCI and slower gait speed (Hsu et al., 2019). In our study cohort, mobility impairment was not reported frequently and there was little change between baseline and follow-up time points in the mobility factor of the BADLS, which would have made it difficult to show an association with changes in functional networks. More recently Luo and colleagues found altered graph metrics in subjects with AD and MCI as compared to healthy controls in a Chinese population, using Chinese brain template. Some of the graph metrics were correlated with clinical variables. ADL was positively correlated with assortativity of the whole brain - a measure reflecting the preference of network nodes to form connections with similar nodes. The increase in assortativity reflects reduced resilience of the neural network, therefore the severity of condition appears to be directly correlated with the reduction of resilience (Newman, 2002). Another metric that was found to be positively correlated with ADL was nodal degree centrality of the frontal regions. Node degree centrality reflects the number of node edges - i.e. connections - and therefore more efficient communication with other parts of the network, implying a compensatory mechanism or activation of brain plasticity in the presence of neurodegenerative process (Guo et al., 2016). The study was conducted in Chinese participants and it is unclear whether the findings are generalisable to other ethnic groups, additionally, the number of

participants within each of three groups (AD n=24, MCI n=27 and healthy volunteers n=33) was quite small.

4.3.2 Connectivity analysis in correlation with neuropsychiatric symptoms

Our approach was a data-driven analysis of brain connectivity using the ICA, which produced spatial maps that we later identified as resting state networks. We focused on four resting state networks, DMN, salience, and left and right frontoparietal networks - these have been previously reported to be altered in AD (Balthazar et al., 2014, Chand et al., 2017, Mendez, 2021). These networks correspond to the large scale brain networks used by Menon in the 'triple network model' that was proposed to understand the cognitive and emotional dysfunction across the range of neurological and psychiatric disorders, including AD (Menon, 2011). The triple network model is based on the three large brain networks - DMN, salience network and central executive network - the latter corresponds to lateralised frontoparietal networks, although there is ambiguity in how the functional networks nomenclature is used by authors in the field of rs-fMRI. In Menon's model, the interaction between task-negative network, DMN, and task-positive salience network was mediated by central executive network (Menon, 2011).

4.3.2.1 Default mode network connectivity and neuropsychiatric symptoms

In the field of Alzheimer's disease research, DMN is the main network of interest, due to numerous and consistent reports of reduced connectivity occurring early in the disease process (Greicius et al., 2004, Rombouts et al., 2005, Buckner et al., 2008). However, the process of DMN disconnection in AD is nuanced and non-linear - for example, in the earlier stages of the disease, a reduced connectivity in the posterior DMN is observed with the corresponding increase in activity in the anterior nodes of the network (Damoiseaux et al., 2012). It has also been reported that pharmacological intervention might increase the activity within DMN, for example following treatment with memantine, an NMDA receptor antagonist, which is a symptomatic treatment for AD (Lorenzi et al., 2011). This finding posits a theory of DMN dysfunction being potentially linked to the dysregulation in glutamatergic system, which is one of the neurochemical mechanisms in AD pathology.

Our study found increased connectivity in the posterior regions of DMN, specifically in

the precuneus and PCC, in correlation with agitation, irritability, sleep and night-time behaviour disorder items of the NPI. We initially hypothesised an opposite direction of this association, in line with the pervading narrative of disconnection within DMN in AD. There is a limited number of publications on the association between DMN connectivity and agitation, although a recent study by Lee and colleagues found that reduced connectivity in the anterior part of DMN was correlated with the severity of hyperactivity sub-syndrome in a study using the seed-based method of investigating resting state networks (Lee et al., 2020). Serra and colleagues have previously showed an increased connectivity between ventral segmental area (VTA) and hippocampus and the cerebellum in correlation with Factor 1 of the NPI (encompassing agitation, irritability and disinhibition and therefore not fully equivalent to the Hyperactivity sub-syndrome considered in this study) (Serra et al., 2018).

Our study also revealed a positive correlation between changes in sleep and night-time behaviours and connectivity in the right precuneus. DMN is a network of interest in sleep disorders due to its task-negative focus (Tian et al., 2020). It has been previously reported that increased connectivity of medial prefrontal cortex to precuneus is associated with poorer sleep quality in healthy middle-aged adults (Song et al., 2016) and cognitively healthy adults with various chronotype patterns (Tian et al., 2020). The opposite direction of association was observed between sleep quality measures and connectivity within DMN in adolescents (Tashjian et al., 2018, Lunsford-Avery et al., 2020). McKinnon and colleagues found reduced functional connectivity in DMN in participants with MCI and nocturnal waking when compared to MCI subjects with normal sleeping pattern (McKinnon et al., 2017). It is likely that the relationship between DMN and sleep in AD is complex, especially as the NPI item captures a variety of sleep disturbance, including features such as excessive sleep in contrast to delineated and specific sleep quality measures, focusing on insomnia, reported in literature.

We have found a negative correlation between connectivity in DMN and the NPI item of appetite and change in eating habits. We found no relevant publications on resting state connectivity within the DMN and appetite and eating habits in AD, but a disruption in DMN connectivity has been previously reported in eating disorders (Steward et al., 2018). Similarly, as with sleep and night-time behaviour item of the NPI, appetite and change in

eating habits captures a wide variety of eating behaviour and therefore may be subject to complex relationship with intrinsic resting state activity in the brain.

The presence of neuropsychiatric symptoms may alter the functional connectivity within the brain and previously it has been established that DMN may show both a reduction and an increase in activity in some psychiatric disorders, such as schizophrenia (Hu et al., 2017). Spatial ICA has been previously used in exploring network connectivity in schizophrenia, where increased activity in elements of DMN was correlated with the severity of positive symptoms of psychosis (Garrity et al., 2007). A study on neuro-feedback in people with a history of psychiatric symptoms vs. healthy controls showed slightly higher DMN centrality in the former group (Skouras and Scharnowski, 2019).

Further example of increase rather than reduction of network connectivity in psychiatric disorders has been reported in patients with schizophrenia who failed to deactivate anterior and posterior medial regions of DMN during facial emotion tasks (Salgado-Pineda et al., 2011). Ng and colleagues found increased 18-fluorodextrose-glucose (FDG) uptake in posterior cingulate cortex (as well as anterior insula and ventral OFC) on PET-CT in people with preclinical AD and higher NPI scores, which reflected increased metabolism in these areas. Whilst at follow-up those individuals presented with hypometabolism in PCC, the initial hyper-metabolism in PCC, which belongs to DMN network, is consistent with our finding of increased connectivity in DMN in people with a higher NPI burden (Ng et al., 2017b).

4.3.2.2 Salience network connectivity and neuropsychiatric symptoms

Salience network is involved in guiding attention based on the integration of sensory input to salient stimuli in order to modulate behaviour. A disturbance in its nodes, such as dorsal ACC and the anterior insula has been reported in previous structural and functional MRI studies in various psychiatric disorders (Peters et al., 2016). Increased salience network connectivity has been correlated to the severity of the Hyperactivity sub-syndrome in AD (Balthazar et al., 2014).

Our study found increased connectivity in the salience network in correlation with the severity of the Affective sub-syndrome of the NPI, as well as anxiety, agitation and

aberrant motor behaviour items. This finding is in agreement with a previous report by Balthazar and colleagues, who found increased activity in the salience network in people with AD as compared to healthy controls, as well as a positive correlation between the hyperactivity syndrome and connectivity in the anterior salience network. Other research groups had previously reported a similar direction of association between salience network and connectivity in the anterior cingulate and the right insula and the severity of symptoms in Hyperactivity sub-syndrome. They also found increased connectivity in salience network in people with AD when compared to healthy controls (Balthazar et al., 2014). Zhou and colleagues found increased connectivity in salience network in AD (and reduced in DMN) but the opposite effect was observed in subjects with bv-FTD.

Altered connectivity within the salience network has also been linked to other psychiatric disorders such as depression, with both increased and decreased connectivity between various network nodes (Brakowski et al., 2017). Xiong and colleagues found increased connectivity in the right STG in subjects with generalised anxiety disorder when compared to healthy controls, although they did not find significant correlation with the severity of anxiety (Xiong et al., 2020). Increased connectivity of anterior insula - one of the regions that we identified as positively correlated with the severity of Affective sub-syndrome and anxiety item of the NPI, has previously been linked to anxiety disorders (Menon, 2011).

4.3.2.3 Frontoparietal network connectivity and neuropsychiatric symptoms

Left and right frontoparietal networks are considered to contribute to the coordination of behaviour in timely, focused and goal driven manner (Marek and Dosenbach, 2018). Together with DMN and salience networks, frontoparietal networks comprised the ‘triple-network’ system that in collaboration manages the internal thought processes and captures the relevant stimuli to engage in focused cognitive control and behavioural response (Menon, 2011).

Similarly, as with other networks, in our study connectivity in the right and left frontoparietal networks correlated positively with the severity of neuropsychiatric symptoms. We have found a positive correlation between connectivity in the right frontoparietal network and total NPI score, Psychosis and Hyperactivity sub-syndromes, as well as in agitation and sleep and night-time behaviour items. Connectivity in left frontoparietal network in our

study correlated positively with Hyperactivity sub-syndrome as well as agitation and irritability items of the NPI.

Dysfunction in frontoparietal networks has been previously reported in psychiatric disorders - an increase in connectivity between left frontoparietal network and left temporal and parietal regions were found in people with schizophrenia and their first degree relatives (Chahine et al., 2017). Disruption and altered connectivity in frontoparietal network has previously been reported in children with attention deficit hyperactivity disorder (ADHD) (Gao et al., 2019, Hua et al., 2021). Matsuoka and colleagues studied the relationship between neuropsychiatric symptoms in MCI and resting state connectivity - they found a negative correlation between the connectivity in left frontoparietal network and total NPS burden as measured by MBI-C (Matsuoka et al., 2021). This finding appears to contrast with the positive correlation between frontoparietal network connectivity and NPI scores found in the group of participants with AD in our study. We have not found correlation in between functional connectivity and neuropsychiatric symptoms in participants with MCI, this may be due to relatively smaller number of participants in this group as well as using different instruments to measure symptoms. Munro and colleagues found decreased connectivity in frontoparietal network in association with higher scores on Affective sub-syndrome of the NPI in participants with MCI (Munro et al., 2015). In contrast, in our study, activity in the right supramarginal gyrus and the right frontal pole within the frontoparietal network correlated positively with the total NPI score, as well as several symptoms and sub-syndromes, but not with the Affective sub-syndrome or with depression or anxiety. These divergent findings may be related to the differences in methodology, such as cross sectional and longitudinal study design. It may also be possible that the symptoms and sub syndromes that correlated positively with the connectivity in frontoparietal networks in our study, such as Hyperactivity and Psychosis sub-syndromes as well as symptoms of agitation, irritability and altered sleep and night-time behaviour have different neural correlates to affective symptoms and therefore may have a different direction of correlation.

4.4 Increased network connectivity in neuropsychiatric symptoms of Alzheimer's disease

Studies using graph theory analysis of people with MCI, AD and healthy controls show

a complex picture with conflicting results relating to small-world properties of the brain in AD. In graph theory, as applied to studying brain connectivity, ROIs play the role of nodes, whilst the connections between ROI - edges. Seo and colleagues analysed brain connectivity using FDG-PET studies of volunteers with AD, MCI as well as those with no cognitive dysfunction. The authors used two basic parameters in network analysis: local clustering and characteristic path length (Seo et al., 2013). Local clustering reflects node's likelihood to have connections with neighbours, expressed as the clustering coefficient. Clustering of a network, expressed as the network clustering coefficient, is the average of clustering coefficients of all its nodes. Network clustering reflects the interconnectivity of the local network (Rubinov and Sporns, 2010). Characteristic path length is the mean minimum number of edges on the shortest path connecting any two nodes in the network. Path length reflects the functional integration of a network (Rubinov and Sporns, 2010).

Both local clustering and characteristic path lengths are used to determine whether a network has properties of a 'small world', which is characterised by high network clustering coefficient and short path. The network meets the criteria of small-world if its clustering coefficient in higher, and path length similar to a matched (generated with the same number of nodes) random network (Watts and Strogatz, 1998). Seo and colleagues used betweenness centrality to characterise local nodes. Betweenness centrality of a node is the number of shortest paths connecting any two nodes in the network that run though that node. Nodes with high betweenness centrality are considered hubs on the localised networks (Seo et al., 2013). The authors observed that there were no statistically significant differences between the group in the small-worldness properties of brain networks or in characteristic path length on the whole. There were, however, differences in local clustering, and whilst both AD and MCI showed lower clustering coefficients than healthy volunteers, the MCI group (and the very mild AD subgroup within AD participants) showed lower local clustering as opposed to participants with AD. The clustering coefficient reflects the closeness of local integration and this appears to be most affected in the MCI stage - the authors speculate this may be related to the regional dysfunction in specific regions, as opposed to a more widespread pattern seen in more advanced AD, where the whole-brain integration may increase. Participants with MCI and AD had decreased normalised betweenness centrality in DMN hubs compared to healthy controls - functional integration decreases progressively, but functional relatedness

between neighbouring brain regions may follow a U-shape curve. Whilst the authors used clinical criteria for diagnosis of AD, the cognitive impairment of participants with AD was much lower as compared with our study - MMSE score of 17, whilst participants with the diagnosis of MCI had the average score of 22 (which is below cut off point for dementia) - this makes this cohort not directly comparable to ours (Seo et al., 2013).

Neuroimaging research performed in other patient populations have shown positive correlation between network connectivity and clinical variables. Phillipi and colleagues studied the relationship between connectivity in DMN, frontoparietal and cingulo-opercular network (which corresponds to salience network) and found a positive correlation between increased connectivity in all three networks and Factor 2 of the psychopathy scale, reflecting lifestyle and antisocial traits (Philippi et al., 2015). A meta-analysis of studies in participants with bipolar affective disorder found reduced connectivity in DMN, both reduced and increased connectivity in the frontoparietal network, increased connectivity in the affective network and ventral attention network (Gong et al., 2021), which demonstrates that altered functional connectivity within network may have two-directional association with the severity of symptoms.

Previous studies have found associations between the disconnection in brain networks - notably the DMN as one of the early processes in the development of AD. In our study, we have found a positive correlation between the severity of various neuropsychiatric symptoms at 3-year follow-up and connectivity in baseline brain networks - this is in contrast to the hypothesised negative correlation. This may be due to a different nature of alterations in connectivity in relation to psychiatric symptoms rather than the neurodegenerative process itself. Previous studies have found decreases as well as increases in network connectivity in conditions such as schizophrenia (Wolf et al., 2011) and autism (Cerliani et al., 2015). Moreover, as demonstrated by Seo and colleagues, the dynamics of change in network connectivity may follow a non-linear pattern and be associated with both increase and decrease along the disease continuum (Seo et al., 2013).

Increased connectivity has been found in frontoparietal or salience networks in other psychiatric disorders - which may explain why an increased connectivity was linked to more severe neuropsychiatric symptoms. In our sample, people with agitation had

increased connectivity in all analysed resting state networks.

Hafkemeijer and colleagues found that connectivity between specific structures such as paracingulate gyrus and salience and frontoparietal network was higher in AD when compared to healthy controls (Hafkemeijer et al., 2017). Additionally, there is a possibility of increasing functional connectivity between network nodes as a compensation mechanism in response to the reduced function in more vulnerable areas. Scouras and colleagues have found in their eigenvector centrality mapping study, that increased connectivity in middle cingulate and precuneus and between PCC and the cerebellum increased as a response to decoupling between the vulnerable regions such as the hippocampus, crus I and in the early stages of AD process. However, general decompensation was observed in subjects in the dementia stage (Skouras et al., 2019). In our study, increased connectivity within the resting state networks was observed in the AD group, but it was correlated positively to the neuropsychiatric symptoms burden.

4.5 Limitations of the study

4.5.1 Participant sample

Participants in our study were recruited from patients who had a clinical assessment in a memory clinic. The diagnoses of AD and aMCI were based on that clinical assessment and the application of published diagnostic criteria (Petersen, 2004, McKhann et al., 2011). However, there was no biomarker confirmation of the AD pathological process, which introduces a possibility of a pathologically heterogenous group, which could have affected the results. The pathological confirmation of the neurodegenerative process is not a routine part of the local memory clinic pathway. Therefore, introducing investigations such as an amyloid PET-CT or CSF analysis would have impacted the feasibility of the study, as it would have required additional funding, or would potentially affect the generalisability of results in the study sample by making it more selective. It is likely that more frail participants may have not been able to tolerate more scanning time or a lumbar puncture.

The dichotomisation of participants into ‘AD’ and ‘non-AD’ groups was based on the clinical diagnosis at the time of the follow-up visit. Whilst the diagnostic category allocated at the

time of follow-up compared to the baseline assessment was more reliable, allowing for the 3-year-follow-up period during which the progression, or stability of clinical presentation was observed, the lack of biomarker confirmation necessitates caution, as it is possible that some participants in the non-AD category might have had a slowly progressing AD pathological process that did not manifest as 'conversion' to dementia at 3 year follow up. Conversely, the AD group could have included participants with clinical presentation of Alzheimer's dementia that was not linked to AD pathological process. Ideally, further studies should include a biomarker confirmation of the pathological process most likely underlying the clinical syndrome, although, considering the frequent overlap of brain pathologies in older people (Schneider et al., 2007), some degree of caution would be warranted even if the presence of amyloid pathology were confirmed.

Most of our participants had a relatively mild degree of cognitive impairment at baseline and consequently little or no functional impairment. This limited the range of scores on the ADL questionnaire and made it probably less likely to find the relationship between brain structure and connectivity and the overall functional decline or changes in specific ADL factors.

This study was based on analyses of existing imaging data, acquired in the course of another study augmented by the collection of follow-up clinical variables. The numbers were fixed by the earlier imaging data and therefore we did not carry out pre-study power calculations. The post-hoc analysis of the study sample completed shows that based on the 65 participants for whom we had adequate quality of the fMRI, at 80% power we would have the ability to identify a medium effect size of 0.33. However, conventional statistical calculations do not readily translate into imaging studies. Power calculation tools for fMRI studies are available, but usually require an a priori determined ROI and apply to event-related fMRI experiments (Mumford, 2012). A small sample size incurs a risk of under powering that may fail to detect a true effect, but it may also overestimate the observed the statistically significant effect (Button et al., 2013), therefore the results of this study need to be interpreted with caution and followed-up by further research.

4.5.2 Factors relating to study design

The Neuropsychiatric Inventory is not part of a routine clinical assessment in the memory

clinic from which our participants were recruited. Thus, we were not able to perform a cross-sectional analysis between brain structure and connectivity and baseline neuropsychiatric symptoms, to examine whether there was any association between network connectivity and the symptoms at baseline. As neuropsychiatric symptoms present periodically and do not necessarily follow a linear trajectory or change like cognitive or functional decline, it is difficult to hypothesise whether looking at the NPI change between baseline and follow up would provide definitive information.

4.5.3 Factors relating to image analysis

The visual rating of clinical images was performed by the same consultant neuroradiologist, thus preventing the issues of inter-rater reliability, but test-retest reliability was not evaluated. The analysis of clinical imaging report data could have been further enhanced by using additional visual rating scales, such as Global Cortical Atrophy scale - a visual rating scale based on the evaluation of sulcal and ventricular dilatation of the frontal, parieto-occipital and temporal regions in each hemisphere and in the third ventricle (Pasquier et al., 1996). The MTA scale that was used to assess hippocampal atrophy is relatively insensitive to early degenerative changes that may be limited to entorhinal cortex (Du et al., 2004). An alternative approach could have included the entorhinal cortex atrophy (ERICA) scale, evaluating atrophy in the entorhinal cortex and the parahippocampal gyrus and the widening of the collateral sulcus and the cleft between the entorhinal cortex and the cerebellar tentorium (Enkirch et al., 2018). The MTA score, which reflects hippocampal atrophy, could have lacked sensitivity in the study cohort consisting of participants who, at baseline, had relatively mild cognitive deficits and who, in substantial proportion, remained at the level of mild cognitive impairment throughout the 3-year-follow-up.

Obtaining good fMRI data from people with cognitive impairment is challenging, and, albeit the resting-state approach removes the need for task compliance, artefacts related to involuntary motion are more likely to occur in this population than in cognitively preserved young participants. Although several approaches for ‘cleaning’ rs-fMRI data have been proposed (Caballero-Gaudes and Reynolds, 2017, Dipasquale et al., 2017), many of these algorithms perform poorly in clinical datasets. The quality assurance procedure set up

resulted in the exclusion of 14 participants for excessive motion.

The nomenclature of the resting state networks is an evolving area. Some networks, such as the lateralised frontoparietal network, have also been referred to as 'central executive network' or 'executive control network', whilst the salience network has been referred to as the ventral attention network, or opercular-cingular network (Uddin et al., 2019). Additionally, consensus is lacking as to which regions contribute to a particular network. It is also recognised that there may be an overlap between networks and regions, such as the anterior insula, which may be involved in many different networks or brain functions (Pessoa, 2014). In our study, we have identified networks that contribute to cognitive functioning as well as emotional and behavioural presentation. This may explain the overlap between regions whose connectivity correlated with the severity of symptoms across various networks.

We have used measures to correct for multiple comparisons at the cluster level, such as FWE in VBM analysis and TFCE for connectivity data. However, we have not corrected for the multiple tests (e.g. correlating each imaging variable with NPI scores) that are performed in the course of this study. The main reason was the exploratory nature of our research and the fact that we cannot assume the independence of variables, as the clinical symptoms such as anxiety and depression, or agitation and irritability that are likely to be related and overlap in a participant.

As described in section 3.2, fMRI is based on the principle of neurovascular coupling, where neuronal activity causes an increase in oxygenated blood flow and the subsequent BOLD contrast. However, BOLD signal may vary according to a number of physiological and pathological factors (Krüger and Glover, 2001, Birn, 2012). The main physiological factors are cardiac and respiratory function (Murphy et al., 2013). Cardiovascular function causes blood and CSF pulsatility, dependent on heart rate, and influence BOLD fluctuations in specific regions, mainly next to ventricles, large perivascular spaces and sulci (Chang et al., 2009). Another source of physiological noise is respiration, which can cause T2* signal change, through the vasodilatatory effect of CO2, or by influencing and worsening motion (Glover et al., 2000). Physiological noise may lead to both false negative results, due to lowering statistical sensitivity, as well as false positive findings (Birn, 2012). There are ways of correcting the influence of respiration and blood pulsatility on BOLD

signal. Some of those measures can be applied at the time of image acquisition, such as measurement of heart rate and oxygen saturation levels with a pulsoximeter, which allows estimation of cardiac and respiratory cycles corresponding to image slices using a method of retrospective image corrections (RETROICOR) (Glover et al., 2000). BOLD fluctuations related to cardiac and respiratory factors can also be removed from acquired imaging data by low-pass filtering to remove high frequency fluctuations, though this will not remove all physiological noise. For event-related fMRI, software packages such as SPM offer a choice of modelling of hemodynamic response function (HRF), including canonical HRF as well as its model derivatives, that combine the canonical HRF with time and dispersion derivatives (Henson et al., 2001). Finally, the variability of the BOLD signal appears sensitive to a number of factors that are relevant in this clinical population. For example, BOLD signal fluctuations may be lower in precuneus and posterior cingulate (nodes of DMN) in people with cognitive impairment (Han et al., 2011), or related to preclinical pathology, such as CSF beta-amyloid and markers of neurodegeneration (Millar et al., 2020), which may have influenced the findings.

4.6 Future directions and applications

Currently, research in network connectivity in AD has had varying and at times conflicting results. It appears possible that specific symptoms or symptom clusters may be associated with varying connectivity alteration patterns and therefore it is important to consider research questions carefully and resist the temptation to extrapolate findings from a study exploring cognitive symptoms to those from the neuropsychiatric spectrum. It is however important to continue with this research as the information about changes in network connectivity may provide biomarker-type evidence that can be helpful in diagnosis, prognosis, or personalised medicine - for example, specific changes in connectivity in executive control network might predict the response to treatment in depression.

Our study identified reduced grey matter volume in the neocerebellum, with clusters centred in the area of crus I and crus II, as potentially predictive of neuropsychiatric symptoms. The role of the cerebellum in the neuropsychiatry of Alzheimer's disease has not been extensively studied, despite previous research indicating involvement in cognitive pathways as well as in regulation of affective symptoms in other psychiatric disorders. One

of the possible avenues of studying the links between the cerebellum and the main brain networks would be to perform a seed-based resting state study with the seed placed in the neocerebellum.

The data presented here supports further research into the use of brain imaging in predicting the progression of symptomatology of Alzheimer's disease and other dementias. To enhance the generalisability of future findings, new studies should endeavour to recruit from population-based memory clinic patients. In order to improve the disease-specificity, it would be helpful to use larger more representative samples and also to include biomarker confirmation of the pathological process. As these become more part of routine clinical practice, this may become more feasible as blood-based biomarkers become more robust and close to translation into clinical practice (Zetterberg, 2019, Hansson, 2021, Keshavan et al., 2021).

4.7 Conclusions

Our study found that regional grey matter volume and alterations in connectivity in resting state networks are associated with the severity of neuropsychiatric symptoms at 3 year follow up. These appear consistent with previous reports of studies in cohorts of people with AD, other neurodegenerative disorders, as well as in younger adults with psychiatric conditions. This finding supports the potential of using quantitative brain imaging as a tool to support prognosis for patients attending memory clinic, especially when combined with machine learning and deep learning protocols that can help with prognostic information for an individual. This approach has already been studied in the context of improving diagnosis and prognosis such as the risk of developing dementia (Dallora et al., 2017, Liu et al., 2018, Li et al., 2019, Ezzati et al., 2019, Graham et al., 2020). The utility of brain imaging to inform prognosis of the risk of developing neuropsychiatric symptoms so far has not been studied in AD - our findings show that this may be one of the variables considered in building comprehensive models of disease progression.

In summary, we found that resting state network alterations appear to predict the development of neuropsychiatric symptoms in Alzheimer's disease. The direction of the correlation between the network connectivity and the severity of NPS has been positive,

which reflects the complexity of changes in intrinsic network connectivity in Alzheimer's disease, where cognitive impairment may be related and in fact predicted by decrease in connectivity in resting state networks such as DMN, but where the neuropsychiatric symptoms appear to correlate to increased connectivity within networks.

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