Personalised medicine for psychotic symptoms in Alzheimer's disease: elucidating mechanisms and improving assessment

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Author's declaration

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Signed: Sara Scarfo

Date: 25/09/2026

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Abbreviations

AD = Alzheimer's Disease

ADAS-Cog = Alzheimer’s Disease Assessment Scale – Cognitive Subscale

ADNI = Alzheimer's Disease Neuroimaging Initiative

ALE = activation likelihood estimate

a-MCI = amnestic Mild Cognitive Impairment

APOE4/ε4 = Apolipoprotein E

AVLT = Auditory Verbal Learning Test

Aβ = Amyloid Beta

BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease Rating Scale

BNT = Boston Naming Test

CAMCOG = Cambridge Cognition Examination

CANTAB = Cambridge Neuropsychological Test Automated Battery

CBMA = Coordinate-Based Meta-Analysis

CDR = Clinical Dementia Rating

CDT = Clock Drawing Test

CERAD = Consortium to Establish a Registry for Alzheimer’s Disease

CFA = Confirmatory Factor Analysis

CFT = Category Fluency Test

CI = Confidence Interval

CIS = Central Insular Sulcus

CN = Cognitively Normal

COWAT = Controlled Oral Word Association Test

CSF = Cerebrospinal Fluid

CT = Computerised Tomography

CUSPAD = Columbia University Scale for Psychopathology in Alzheimer's Disease

CV = Cross Validation

CVLT = California Verbal Learning Test

DLPFC=Dorsolateral Prefrontal Cortex

DMN = Default Mode Network

DRS = Dementia Rating Scale

DSM = Diagnostic Statistical Manual

DSST = Digit Symbol Substitution Test

FAB = Frontal Assessment Battery

FAQ = Functional activity questionnaire

FDG-PET = Fluorodeoxyglucose Positron Emission Tomography

FDR = False Discovery Rate

fMRI = functional Magnetic Resonance Imaging

FTD = Frontotemporal Dementia

FWE = Family Wise Error

GCA-F = Global Cortical Atrophy-Frontal

GDS = Geriatric Depression Scale

HVLT = Hopkins Verbal Learning Test

ISTAART = International Society to Advance Alzheimer's Research and Treatment

IWG = International Working Group

JBI = Joanne Briggs Institute

JDR = Join Dementia Research

KDA = Kernel Density Analysis

LASSO = Least Absolute Shrinkage and Selection Operator

LBD = Lewy Body Dementia

LFT = Letter Fluency Test

MAE = Mean Absolute Error

MATLAB = Matric Laboratory

MBI = Mild Behavioural Impairment

MBI-C = Mild Behavioural Impairment - Checklist

MCB = Modified Confabulation Battery

MCI = Mild Cognitive Impairment

MDI = Mean Decrease in Impurity

MFTC = Multiple Features Targets Cancellation

MKDA = Multilevel Kernel Density Analysis

MMSE = Mini Mental State Exam

MNI = Montreal Neurological Institute

MOCA = Montreal Cognitive Assessment

MRI = Magnetic Resonance Imaging

MTA = Medial Temporal Lobe Atrophy

NIA-AA = National Institute on Aging–Alzheimer’s Association

NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NOS= Not Otherwise Specified (dementia)

NPI = Neuropsychiatric Inventory

NPIA = Neuropsychiatric Inventory (delusions)

NPIB = Neuropsychiatric Inventory (hallucinations)

NPI-Q = Neuropsychiatric Inventory - Questionnaire

NPS = Neuropsychiatric Symptoms

NPV = Negative Predictive Value

OR = Odds Ratio

OSF = Open Science Framework

PA = Posterior Atrophy

PCA = Principal Component Analysis

PET = Positron Emission Tomography

PPIE = Patient and Public Involvement and Engagement

PPV = Positive Predictive Value

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RAVLT = Rey Auditory Verbal Learning Test

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status

rCBF = Regional Blood Flow

rCMRglc = Regional Cerebral Metabolic Rate Of Glucose

rel-CBF = Relative Regional Cerebral Blood Flow

RF = Random Forest

RMSEA = Root Mean Square Error of Approximation

ROCF = Rey-Osterrieth Complex Figure

ROI = Region of Interest

RPM = Raven's Progressive Coloured Matrices

SAD = Sum of Absolute Differences

SBM = Surface-Based Morphometry

SD = Standard Deviation

SPECT = Single Positron Emission Tomography

SPM = Statistical Parametric Mapping

SPSS = Statistical Package for Social Sciences

SQ = Symptomology Questionnaire

SRMR = Standardised Root Mean Square Residual

SVD=small vessel disease,

TIV = Total Intracranial Volume

TMT = Trail Making Test

VaD/VD=vascular dementia,

VBM = Voxel-Based Morphometry

VIF = Variance Inflation Factor

WAIS = Wechsler Adult Intelligence Scale

WCST = Wisconsin Card Sorting Test

WISC = Wechsler Intelligence Scale for Children

WMC = White Matter Changes

WMH = White Matter Hyperintensities

WMS = Wechsler Memory Scale

Abstract

Psychotic symptoms (delusions and hallucinations) are among the most prevalent and impactful neuropsychiatric symptoms of Alzheimer's disease (AD), being associated with serious adverse outcomes which make them important targets of investigation. This thesis aims to explore the underlying mechanisms of different manifestations of psychotic symptoms in AD, and to propose a novel digital tool to improve their monitoring.

Addressing the first aim, two systematic reviews and a series of studies, using secondary data made available from the ADNI database (adni.loni.usc.edu), were performed, proposing novel methodological and analytic approaches. Study 1 investigated the stability of a neuropsychiatric symptoms clusters: results indicated that while a psychotic cluster can be identified, this is not stable, and the patterns of association with other neuropsychiatric symptoms are dependent upon disease progression. Through the first systematic review and the related Study 2, neuroanatomical correlates and predictors of psychotic symptoms in AD were investigated, broken down into delusions and hallucinations, and the thematic subtypes misidentification and paranoia. These indicated that while certain brain areas appear to be linked to all psychotic symptoms, distinct patterns appear in association with specific manifestations. The second systematic review and the related Study 3 identified comparable findings from a cognitive perspective, as psychosis as a cluster was associated with overall greater cognitive dysfunction while clearer profiles emerged looking at the individual symptoms and themes. On the basis of the findings of the previous studies and systematic reviews, Study 4 employed a machine learning technique, Random Forest analysis, to propose potential multi-modal markers of a psychosis phenotype in AD.

Lastly, addressing the second aim, Study 5 introduced a new digital tool which allows for a frequent monitoring of psychotic symptoms in AD, adding novel elements to current assessment strategies, including capturing daily symptoms fluctuations, and timely identification of potential triggers and symptoms co-occurrences.

Chapter 1. Prevalence and phenomenology of psychotic symptoms in Alzheimer's disease

1.1. Overview

This chapter aims to introduce the research on psychotic symptoms in Alzheimer's disease. Specifically, it provides information on the population that is the focus of this thesis, that of people presenting with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI), introducing the neuropathology and clinical presentation of AD and focusing on the importance of early assessment and the concept of biomarkers. It then proceeds to outline neuropsychiatric symptoms (psychiatric and behavioural manifestations which constitute core symptoms of AD dementia and MCI), focusing on the currently available assessment methods, symptom prevalence, clinical manifestation, and impact on disease trajectory. Within these, greater attention is given to psychotic symptoms (delusions and hallucinations), which represent key areas of investigation of this thesis. While describing the phenomenology of psychotic symptoms, definitions and theoretical frameworks are provided, introducing a novel approach to the classification of these symptoms. The chapter ends discussing the current gaps in the literature in this research area, with particular attention to new and innovative ideas for predictive studies, based on machine learning methods, and personalised assessment, finally leading to the rationale, aims, objectives and structure of this thesis.

1.2. Introducing Alzheimer's disease

AD is the leading neurodegenerative disease and the most common form of dementia, presented by approximately two thirds of the cases (*2025 Alzheimer's Disease Facts and Figures*, 2025; World Health Organization, 2025): it affects an estimated 36 million out of the 55 million people living with dementia in the world (Alzheimer's Disease International, 2025). While dementia caused by AD pathology is the most common form of dementia, dementia is a syndrome that can have multiple possible causes, leading to the deterioration of cognitive functions beyond what might be expected from the usual consequences of biological ageing (World Health Organization, 2025). Causes for dementia other than AD are introduced below (at the end of this section).

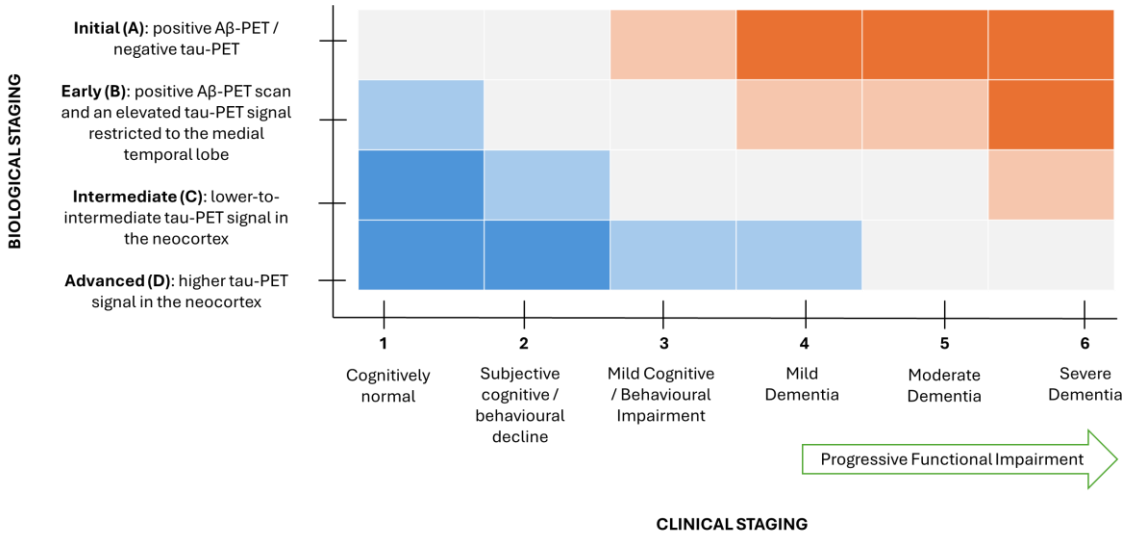
AD is a degenerative brain disorder, characterised by progressive intellectual and behavioural deterioration, with its most distinctive neuropathological markers identified by the accumulation of plaques formed by the misfolded extracellular protein fragment beta-amyloid (Aβ) and the intracellular neurofibrillary tangles of abnormal hyperphosphorylated tau aggregates in the brain (Mandell & Green, 2011). These neuropathological events, which can begin up to about twenty years before the overt manifestation of clinical symptoms (*2025 Alzheimer's Disease Facts and Figures*, 2025; Jack et al., 2018; Sperling et al., 2011; Villemagne & Chételat, 2016), lead to neuronal loss and neurotoxicity, brain atrophy, cognitive and functional decline and eventually death (due to serious related complications, among which pneumonia is the most common) (DeTure & Dickson, 2019; Duke Han et al., 2017; Huber et al., 2018; van Oostveen & de Lange, 2021). For this reason, AD is currently conceptualized as a continuum of neuropathological and clinical events (Figure 1.1) which succeed and overlap each other in a multifaceted process, with no firm boundaries between the various clinical stages and with individual variation along the continuum (Aisen et al., 2017; Caselli et al., 2017; van Oostveen & de Lange, 2021). The presence of Aβ and phosphorylated tau can be detected through two types of biomarkers: imaging, with Positron Emission Tomography (PET), and fluid, with cerebrospinal fluid (CFS) and more recently blood collection (Porsteinsson et al., 2021; Thal et al., 2025). With regard to the progress of the pathology across brain areas, a consensus view is that proposed by Braak and Braak (1991), an histopathologic staging system to describe the progressive neurofibrillary tangles distribution in the brain of typical AD, according to which there are six hierarchical stages clearly identifiable in the brain. Stages I and II are marked by the involvement of the transenthorinal and entorhinal cortices, respectively; at stage III, damage is seen in the hippocampus, amygdala, and adjacent neocortical areas while in stage IV the pathologic process extends to neocortical association areas; stage V shows a broader impairment of neocortical association areas, especially in temporal, parietal, and associative occipital regions and lastly in stage VI, degeneration spreads to primary motor and sensory fields.

At a clinical level, the presentation of AD dementia has been historically associated with: 1) a progressive cognitive decline, particularly in the memory domain, as well as language, visuospatial ability, processing speed, attention, executive functions and motor skills (Caselli et al., 2017; Duke Han et al., 2017); 2) a progressive decline in the

ability to perform daily life activities (D'Onofrio et al., 2017); 3) a range of neuropsychiatric and behavioural symptoms (Rose et al., 2025).

Figure 1.1

Clinical and biological staging of AD



Notes. The figure represents the neuropathological and clinical continuum covering both the preclinical (typically clinically asymptomatic individuals with evidence of AD pathology) and clinical (symptomatic) phases of AD, and it has been adapted from Hansson and Jack (2024) (reproduced with permission from the journal Nature Aging, license agreement number 6217520773596). As explained in the model proposed by Hansson and Jack (2024), individuals with typical AD presentation are expected to fall within the grey areas (i.e., neuropathological biomarker Aβ can be detected in advance to clinical presentation, and moderate and severe dementia correspond to tau-PET spread from the medial temporal lobe to the neocortex); dementia in the absence of evident tau-PET signal is likely to be concomitant with other brain pathologies (red areas), while individuals who do not present any or present extremely mild cognitive symptoms at higher tau-PET levels are likely to have high cognitive reserve (blue areas), allowing them to continue to function despite the neuropathological load. The functional impairment that characterises the dementia stages ranges from requiring assistance to maintain independence (mild), requiring assistance with daily tasks (moderate) and requiring assistance with self-care (severe) (Jack et al., 2018).

As shown in Figure 1.1, the AD continuum is typically characterised by a long preclinical phase. This typically starts around 60 years of age and lasts between ten and twenty years (Jack et al., 2024); in this phase the toxic fragments amyloid beta (Aβ) are created and accumulate in specific areas of the brain extracellularly, damaging neuronal synapses, and eventually precipitating into misfolded neuritic plaques in a process that

kills neurons and disrupts neuronal networks (Mandell & Green, 2011). At this stage of localised neuronal loss, individuals might start to experience and report subjective cognitive and/or behavioural decline. As pathology spreads through other brain areas, at a clinical level this is reflected in a prodromal phase of disease, normally referred to as Mild Cognitive Impairment due to underlying AD pathology, at times accompanied by Mild Behavioural Impairment (both are further explained below in section 1.2.2). Lastly, at advanced stages of pathology, a dementia phase may be experienced, which is progressively characterised by mild, moderate, and severe cognitive, functional and behavioural impairment (*2025 Alzheimer's Disease Facts and Figures*, 2025).

The clinical symptoms of AD typically manifest after the age of 65; however, in a small percentage of cases, they can manifest earlier: this has led to the definition of early onset (rare) and late onset (typical) AD. Early-onset AD is generally a familial disorder, while most cases of late-onset AD tend to be sporadic (Atwood & Bowen, 2015). However, a genetic component, the apolipoprotein E (APOE) ε4, has been identified as a risk factor for late-onset AD, as is it associated with increased β-amyloid deposition and thus enhanced risk of developing AD (Tenchov et al., 2024). Studies have in fact shown that people who carry one allele are 3-4 times more likely to develop AD, while presenting two ε4 alleles (homozygous APOE4 carriers) increases the risk 15-fold (Palmer et al., 2023). AD is a heterogeneous disorder, with multiple genotypes and phenotypes which are linked to complex and distinct cognitive, neurological, neuropsychiatric and functional profiles of impairment (Arnold et al., 2024; Duara & Barker, 2022). This heterogeneity of pathological processes and clinical presentation has substantial implications for the advancement of personalised approaches to assessment and symptoms management, and is further introduced below in this thesis.

Lastly, as mentioned above, it is important to note that while dementia caused by AD pathology is the most common, dementia is a syndrome that can have multiple possible causes, leading to the deterioration of cognitive functions, accompanied, and occasionally preceded, by functional decline, as well as changes in mood, emotional control, behaviour, or motivation (World Health Organization, 2025). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), dementia, or major neurocognitive disorder, refers to a condition characterised by a significant decline in cognitive functioning that interferes with daily

living activities, and it is associated with various underlying medical conditions. Other causes for major neurocognitive disorders, or dementia, in addition to AD include cerebrovascular disease (vascular dementia), frontotemporal degeneration, Lewy Body disease and Parkinson's disease, presenting with different clinical profiles (*2025 Alzheimer's Disease Facts and Figures*, 2025). It is not infrequent, however, to present with "mixed dementia": this refers to the presence of concurrent brain pathologies in addition to the biological changes typical of AD, which might contribute to the aggravation of the clinical syndrome (Jack et al., 2024). This is important to consider, in light of a correct assessment and consequent therapeutic interventions: accurately differentiating between AD and other major dementia syndromes (Karantzoulis & Galvin, 2011) can help determine the care, treatment and support services appropriate for the specific disease underlying the dementia (Alzheimer's Association, n.d.).

1.2.1. AD assessment and diagnosis

Historically, Alzheimer's disease could only be diagnosed post-mortem (Ballard et al., 2011). In fact, until the very recent refinement of the Aβ and tau biomarkers which now make it possible to effectively diagnose AD in vivo (Jack et al., 2024), the diagnosis of AD could only be "probable" or "possible", as defined by the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria (McKhann et al., 1984), and it was purely based on the clinical assessment, comprising of individual history, impairment on at least two cognitive functions and progressive nature of the cognitive decline. Subsequently, the International Working Group (IWG) (Dubois et al., 2014; Dubois et al., 2024), formed with the aim of revising this previous set of criteria, and in parallel the National Institute on Aging–Alzheimer's Association (NIA-AA) (Jack et al., 2018; McKhann et al., 2011; Sperling et al., 2011) considered research and clinical findings over the past four decades, incorporating the latest discoveries.

Despite presenting with some conceptual differences (Dubois et al., 2014; Frisoni et al., 2011; McKhann et al., 2011), both groups have proposed new criteria over time, with the overarching aims of enabling early and accurate diagnosis through biomarker support to facilitate early therapeutic trials and incorporating the latest scientific insights (van der Molen et al., 2025). Their major advancement includes bringing the focus on imaging and fluid-based biomarkers to increase diagnostic accuracy, and to extend the AD

neuropathology diagnosis to preclinical and prodromal stages (Dubois et al., 2014; Jack et al., 2018).

The latest criteria proposed by the Alzheimer's Association as a bridge between the clinical and research criteria (Jack et al., 2024) postulate that a diagnosis of disease should be made on the basis of biological changes, as shown in Figure 1.1. Recent innovations in the refinement of biomarkers of AD pathology, included the introduction of blood-based biomarkers (Palmqvist et al., 2024) in addition to the previously available imaging and cerebrospinal fluid (CSF) biomarkers, have in fact made it possible to base the diagnosis on the neuropathological changes described above. Within this framework, it is explained that the clinical syndromes seen with AD are a result of the disease process, and the diagnosis of AD neuropathology is conceptually separate from that of AD dementia (i.e., dementia that is caused by AD neuropathology). However, referring to the stages of Figure 1.1, this group explains that currently, an assessment for AD is typically requested when stage 2 or further are reached, i.e., when a decline from previous levels of cognitive and neurobehavioral function are present, for a consistent period of time (at least 6 months). This can be either documented by a subjective report, a subtle decline on longitudinal testing or a recent-onset behavioural change (e.g., mood, anxiety or motivation) (Jack et al., 2024). The use of AD biomarkers is currently only recommended from stage 3 onwards, to be used together with other relevant assessments (i.e., brain imaging, cognitive, psychiatric and neurological) (Hansson & Jack, 2024).

The criteria proposed by the IWG (Dubois et al., 2024) advocate towards the use of biomarkers to evaluate the risk of future cognitive decline and put in place risk reduction strategies, however compared to the NIA-AA group, they explicitly discourage diagnosing AD pathology in the absence of clinical symptoms, in clinical contexts. This recommendation is based on the concept that, while prevention and treatment strategies to slow down the pathological and clinical decline are starting to emerge, a definite cure is currently not available: disclosing a diagnosis in the absence of an effective treatment might hinder the ethical principle of non-maleficence since the early diagnosis could cause emotional harm to the person (Vanderschaeghe et al., 2018).

In synthesis, while consensus has not been reached yet on all aspects and priorities of how the diagnostic process should be approached, both working groups agree on the

notion that while the clinical presentation alone does not warrant a diagnosis of AD neuropathology, in clinical practice the clinical assessment, based on the person's history as well as neuropsychological and behavioural screening, is still central (Aisen et al., 2017). In this context, the development of precise assessment tools that allow to capture those early cognitive and behavioural manifestations is central to the future research in AD.

1.2.2. Mild Cognitive Impairment, Mild Behavioural Impairment, and the importance of a timely diagnosis

Recent years have seen an emergence of disease modifying therapies (i.e., treatments that aim to alter the trajectory of the disease by impacting the underlying biology of AD rather than focusing on symptom management) (Sims et al., 2023; Van Dyck et al., 2023; Zhang et al., 2025) and secondary prevention projects (a specific set of interventions focused on the earliest stages of AD, before any symptoms have become apparent) (Saunders, Gregory, et al., 2022). As these have higher chances of being effective at a preclinical phase of the disease to prevent further development of the pathology (Avila-Villanueva & Avila, 2024; Suzuki et al., 2017), a worldly effort has been seen to improve early detection of at-risk individuals through application of the biomarkers seen above (Creese & Ismail, 2022). Because of this, achieving consensus definitions of cognitive and behavioural decline that might indicate heightened risk of future development of dementia is currently a research priority. As shown in Figure 1.1 (stage 3), this decline in cognition and/or behaviour in the absence of symptoms that would warrant a diagnosis of dementia has been defined as Mild Cognitive and Mild Behavioural Impairment. While Mild Cognitive Impairment (MCI) has been established more than two decades ago as a diagnostic entity (Petersen, 2004) characterised by objective cognitive impairment and preserved daily functioning (Galati et al., 2025), the notion of Mild Behavioural Impairment (MBI) is much more recent (Creese & Ismail, 2022), however deriving from the research into neuropsychiatric symptoms spanning over the past three decades (Cummings et al., 1994). It has been in fact suggested that their association with cognitive decline at preclinical stages of AD, and their associated risk for future development of dementia, makes neuropsychiatric symptoms potential important markers to consider at early stages of disease (Creese & Ismail, 2022).

Research into Mild Cognitive Impairment began by defining MCI as the clinical condition between normal ageing and AD, typically characterised by impairment in memory that is greater than what expected based on the age, without however meeting criteria for AD (Petersen et al., 2001). Since this early definition, further characterisations of MCI have been made to go beyond memory impairment and extend it to other cognitive functions. This has led to the introduction of criteria to determine amnestic and non-amnestic MCI, as well as single and multiple domain MCI, based on the presence of one (either memory or another) or multiple domain(s) affected (Petersen, 2004). The criteria based on Petersen's work (Albert et al., 2011; Petersen, 2004) include an assessment of the personal history which evidence self- or informant-reported cognitive complaint, objective impairment in one or more cognitive domains, ideally through a complete neuropsychological assessment, preserved or minimally impaired daily functioning, in the absence of dementia. As highlighted by Petersen et al. (2018) diagnosis of MCI is based on the clinical evaluation which determines the cognitive and functional status, and not solely on test scores. Other approaches to assessment have been proposed (e.g., Jak et al., 2009) that are purely based on neuropsychological criteria and do not rely on subjective cognitive decline. However, the role of subjective cognitive decline initially identified appears of relevance as a predictor of future cognitive and functional decline (Ismail et al., 2021; Jessen et al., 2020) so its importance has been confirmed as informative of the person's status (Petersen et al., 2018). While a more extensive neuropsychological assessment appears to provide greater diagnostic precision (Bondi et al., 2014; Galati et al., 2025), the use of a standardised battery is not currently a requirement in the clinical practice. Research is ongoing (Galati et al., 2025; Rye et al., 2022) with the goal of establishing consensus on the assessment, and clarity on the features that are associated with a stability of the diagnosis over time, and importantly, the rate of conversion to dementia (which is discussed below at the end of this section).

A large body of evidence (e.g., Grassi et al., 2019; Quaranta et al., 2023; Rye et al., 2022) in recent years has focused on identifying predictors of conversion from MCI to AD dementia, among which of historical relevance cognitive function, functional ability and neuroanatomical features have been given great attention. Beside these, the presence of neuropsychiatric symptoms at preclinical stages has also been recently suggested as a further risk factor of conversion to AD dementia in preclinical populations (Ismail et al., 2021; Mallo et al., 2020; Roberto et al., 2021), based on the notion that

neuropsychiatric and behavioural symptoms may appear before dementia becomes established, and their presence at this stage can indicate neuropathological disruption of brain networks. Furthermore, certain neuropsychiatric symptoms among which, for example, depression (Rose et al., 2025) and psychotic symptoms (Fischer & Aguera-Ortiz, 2018), when present before AD onset, have also been found to be risk factors for AD: it is important to consider this aspect in the context of clinical assessment, and to reflect on the importance of investigating the nature of these symptoms also prior to the manifestation of cognitive symptoms.

This has led to the proposition of the label “Mild Behavioural Impairment” (MBI) (Ismail et al., 2016), to characterise people with early manifestation of neuropsychiatric symptoms (Geda et al., 2014), who are in a prodromal stage of the disease, similar to how Mild Cognitive Impairment is used to describe people with cognitive problems whose symptoms do not warrant a diagnosis of dementia. MBI is defined as a later-life onset neurobehavioral syndrome; this may emerge at any point along the continuum as shown in Figure 1.1, from normal cognition to subjective cognitive decline through to MCI (Creese & Ismail, 2022). As such, it has been proposed to complement MCI by highlighting late-life emergent behaviours that can reflect neurodegeneration. The research has highlighted that these symptoms might be reported by people without cognitive impairment, who will later develop MCI and AD, therefore a consistent screening has been proposed, which has the potential to function as an early marker of future development of dementia (Ismail et al., 2023; Jin et al., 2023). Criteria for a diagnosis of MBI (Ismail et al., 2017) have been defined by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) (Alzheimer's Association, 2026), requiring a change in the behaviour or personality in at least one of these five domains: decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness and abnormal perception or thought content. These changes should produce impairment in interpersonal relationships, social, or workplace functioning, without meeting criteria for a dementia syndrome. Importantly, MCI and MBI can be concurrently diagnosed. According to these criteria, a Mild Behavioural Impairment Checklist has been developed to capture these symptomology (this is presented below, in section 1.3.1). The emergence of this novel diagnostic entity and the current inclusion of behavioural symptoms at preclinical stages in the newly developed AD criteria reflects a body of research into neuropsychiatric symptoms that

has highlighted their potential to manifest at all stages of the AD continuum and their association with MCI and dementia (Banks et al., 2014; Blasutto et al., 2025; Geda et al., 2014; Köhler et al., 2013; Wise et al., 2019).

In synthesis, as shown above in Figure 1.1, MCI/MBI represent the stage when clinical symptoms begin to be subjectively and objectively present, however they have not yet reached the stage or diagnostic threshold to warrant a diagnosis of dementia. Recent studies focused on early interventions appear promising, suggesting that interventions that target early neurodegenerative processes before irreversible damage has occurred have potential to preserve cognitive functions (Nathan et al., 2025; Rajanna et al., 2025). Furthermore, working on modifiable risk factors such as lifestyle changes (e.g., medications to treat other medical conditions such as diabetes or hypertension, healthy diets, physical and cognitive activity, the role of loneliness and interpersonal relationship) at this stage may confer a protective effect, delaying the onset of AD (Di Marco et al., 2014; Wang et al., 2024) and potentially having a beneficial effect on brain health overall (Parra et al., 2019; Saunders, Ritchie, et al., 2022; Saunders et al., 2018). In this light, the need to accurately identify the individuals at risk of AD dementia and who would therefore benefit from early intervention, is paramount (Rye et al., 2022). In fact, the rates of conversion from MCI/MBI to dementia can greatly vary, and progressing to dementia is only one of the possible outcomes. According to a recent systematic review and meta-analysis which included studies based in several countries in the world (Salemme et al., 2025), with mean follow-up periods of 5.2 years (ranging from 2.7 to 15 years across the studies), the risk of conversion from MCI to AD dementia ranged from 21% (in population-based studies) to 35% (in clinical settings); on the other hand, 50% remained cognitively stable (in both population studies and clinical settings), and 8% (in clinical settings) to 28% (in population-based studies) reversed to normal cognition. While similar data is not yet available for MBI due to it being still quite a recent concept, one of the main reasons for the development of such a diagnostic entity alongside MCI is that presenting MBI alongside MCI is associated with a lower rate of regression to normal cognition and stability than MCI without MBI, and a higher rate of conversion to dementia (McGirr et al., 2022), suggesting the importance of early and consistent monitoring of these symptoms.

1.2.3. Neuroanatomical and cognitive features of AD

As discussed in the previous sections, while modern biomarkers allow detection of AD pathology at preclinical stages, in clinical practice it is not until stages 2 or 3 are reached that help is sought by the person presenting with initial symptoms and in this sense, the biological diagnosis is meant to assist the clinical evaluation (Jack et al., 2024). Therefore, within research and clinical context over the last decades, in parallel to the innovations in the approach to biomarkers to confirm AD pathology, it was fundamental to be able to build a phenotypic profile of AD at earlier stages to identify at risk individuals. Despite the importance of biomarkers to achieve an accurate diagnosis and activate early symptom-management and intervention strategies (Porsteinsson et al., 2021), these are not intended to supplant the clinical assessment, which is still at the core of the assessment process (Aisen et al., 2017; Dubois et al., 2024; Duke Han et al., 2017). Identifying a profile based on cognitive, functional and behavioural features is necessary to activate further investigation with the use of imaging as well as blood and cerebrospinal fluid-based biomarkers, as it is currently not recommended to screen asymptomatic people for clinical purposes (for the reasons discussed above) (Dubois et al., 2024; Jack et al., 2024; Porsteinsson et al., 2021; van der Molen et al., 2025).

In this section, the phenotypic profile of AD along its continuum is introduced from a cognitive, functional, and neuroanatomical perspective. The behavioural perspective, through the study of neuropsychiatric symptoms is discussed in the next section (1.3), while the following one (1.4) specifically focuses on psychotic symptoms (i.e., delusions and hallucinations). In fact, neuropsychiatric, and within these specifically psychotic symptoms constitute the main object of investigation of this thesis, which primarily aims to 1) clarify the patterns of associations with other neuropsychiatric symptoms (explored in chapter 2), the neuroanatomical and cognitive features relating to psychotic symptoms (chapters 3 to 7) and 2) to improve the assessment of psychotic and other neuropsychiatric symptoms (chapter 8). Therefore, aim of this section is to clarify the cognitive functions and brain areas that tend to be associated with AD, and MCI due to AD, in general. In later chapters of this thesis, comparisons are drawn within the population of people with AD dementia and MCI due to AD, between those presenting and not presenting with psychotic symptoms. This is done by introducing the main cognitive functions that are impaired in AD with their associated brain atrophy patterns

(Frisoni et al., 2025; Poulakis et al., 2018) (investigated with the use of imaging techniques such as the PET described above, and the structural and functional Magnetic Resonance Imagining (MRI and fMRI) (Killiany, 2011)). Furthermore, as well as describing typical AD presentation, atypical AD variants are also introduced.

A decline in memory has been historically considered one of AD core clinical features, typically identifiable at very early stages of disease as it tends to be, in typical AD phenotypes, among the earliest cognitive function to be impaired (Jack et al., 2019). Within the memory domain, the main focus has been on episodic memory deficits (Launay et al., 2023), i.e. the difficulty to recall specific events and experiences (further information and definitions of cognitive functions are presented in chapter 5 of this thesis). Episodic memory in AD is normally assessed by free and cued recall tests (Dubois & Albert, 2004; Frisoni et al., 2025; Wagner et al., 2012), indicative of neuropathological changes present in medial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex), areas critical for long-term episodic memory (Dubois & Albert, 2004). Alongside verbal episodic memory, spatial episodic memory plays a key role, reflective of hippocampal neuronal loss (Chan et al., 2016). Traditionally, a decline in the episodic memory function, explained by localised neuronal loss, has been considered as an early and typical sign of AD pathology, playing a central role in the diagnostic criteria mentioned above for AD dementia and MCI due to AD (Albert et al., 2011; Dubois et al., 2014). It has also been suggested that early impairment of episodic memory in people with MCI mediates the effect of neuropathology on an individual's awareness of disease, thus providing an explanation for the development of anosognosia (deficit of awareness) in the prodromal stage as an inability to update insight into their cognitive performance (Gagliardi & Vannini, 2021).

Despite its undoubted role in individuals with AD, episodic memory's central position (particularly the verbal component) has progressively started to be questioned, based on research repeatedly highlighting the relevance of other important, underassessed, cognitive functions (Harrison, 2022).

In line with this, still within the memory domain but moving on from episodic memory, newest research into the insidious nature of cognitive impairment, investigating earlier signs of a future decline have suggested that a potentially earlier marker could be semantic memory (Venneri et al., 2019). It has been in fact suggested that an impairment

in semantic memory might precede episodic memory, mirroring the initial spread of the disease in the transenthorinal and perirhinal cortex, which are strongly associated with lexical-semantic parameters, particularly in individuals presenting with MCI due to AD (Venneri et al., 2011; Venneri et al., 2008). Different measures of semantic memory, such as the category fluency test, based on context-free semantic retrieval, could be used to identify at risk individuals with greater accuracy compared to standard episodic memory tests (Loewenstein et al., 2017; Venneri et al., 2019; Wright et al., 2023), or it could at the least be a complementary assessment procedure.

In addition to long-term memory deficits, another core aspect of memory which is affected by AD is short-term memory, i.e., the temporary storage of information (typically verbal or visual) that is actively being processed, experienced in AD dementia and amnestic MCI (Smith et al., 2025; Zokaei et al., 2020). Recent studies investigating the role of short-term memory at preclinical and prodromal stages have evidenced the role of a function called “visual short-term memory binding”, assessing context-free visual memory, as an early marker of subjective cognitive decline and MCI (Koppara et al., 2015; Parra et al., 2022). As outlined in the above paragraph, the sub-hippocampal atrophy involving entorhinal and perhinal cortices typically affected at earliest stages of disease is associated with context-free memory (Didic et al., 2011), therefore tests such as the Visual Short-Memory Binding Test (Parra et al., 2010) are considered effective at identifying AD at early stages of disease pathology.

Furthermore, recent research has highlighted the relevance of spatiotemporal orientation, i.e. the ability to orient in time and space: while clear disorientation (both in space and time) tends to be more evident within dementia (Tenchov et al., 2024), early signs particularly concerning difficulties with spatial orientation have been noticed in individuals with MCI, and these have been linked to reduced brain activity in temporo-parietal areas (Coughlan et al., 2018; Peters-Founshtein et al., 2023).

In addition to the memory loss, individuals with MCI and AD may experience “false memories”, detailed and vivid memories of episodic events that did not take place (El Haj, Colombel, et al., 2020). These are related to the episodic memory processes in particular the recollection-based monitor process, through which information is retrieved to decide if an event is false (Testo et al., 2025), but fall mostly within the domain of executive functions such as inhibition (in the inability to suppress irrelevant

information) and binding (in the difficulty to hold contextual information together when retaining contextual details associated with an event).

Executive functions' processes are indeed among the main ones to be affected in addition to, or other than, memory, in individuals with MCI and AD dementia. Overall executive dysfunction is highly prevalent in AD, and its severity is associated with worse overall cognitive, neuropsychiatric and functional status (Stokholm et al., 2006; Swanberg et al., 2004). At earlier stages, impairment in executive function tends to manifest as a difficulty to perform tasks that require planning, decision-making, and problem-solving (Tenchov et al., 2024) as well as, as seen above, inhibition and contextual binding (Testo et al., 2025). Subsequently, issues may arise with tasks relating to further processes such as working memory, sequencing and shifting, self-monitoring, flexibility, concept formation and reasoning. As disease progresses, marked dysfunction tends to become significant in most people with AD, and it substantially impacts on activities of daily living (Allain et al., 2013; Daigle Katrina et al., 2022). While executive function has been typically linked to frontal brain areas, more recently it has been suggested that other areas are involved in the regulation of these processes (Daigle Katrina et al., 2022; Lezak et al., 2012; Stuss & Alexander, 2000). A profile of early executive dysfunction particularly in areas of planning, judgement and problem-solving, may indicate the presence of a variant of AD, which based on this historical link between frontal areas and executive dysfunction has been typically referred to as "frontal variant" (Vora et al., 2025); more recently, to encompass the involvement of other regions, it is normally referred to as "behavioural/dysexecutive variant" (Ossenkoppele et al., 2015; Townley et al., 2020). Neurodegeneration has been predominantly identified in frontal (Li et al., 2020; Wolk, 2013) and temporo-parietal (Ossenkoppele et al., 2015) areas, and it is thought to lead to the executive and behavioural difficulties. This variant is typically characterised by a prominent dysexecutive syndrome with less pronounced impairment in memory and other cognitive functions, and the presence of behavioural symptoms such as social disinhibition, apathy, loss of empathy, disregard of social and societal norms, obsessive-compulsive behaviours and psychotic symptoms (Polsinelli & Apostolova, 2022). The relationship between executive function and neuropsychiatric symptoms are further explained below in section 1.3.

Another key function that is typically affected along the AD continuum is attention: impairments can be noticed at earlier (MCI and mild dementia) stages, typically alongside memory, and when present, are related to greater degree of conversion to AD dementia (Testo et al., 2025). Similarly, processing speed, that already tends to decrease with ageing (Harvey, 2019), is affected in AD, and a clear decline can be noticed in advance of global cognitive impairment (Haran et al., 2025). Both attention, particularly sustained (Allain et al., 2013), and processing speed tend to continue to decrease over time at more advanced disease stages, where there is more advanced cognitive decline across most functions, and spread brain atrophy (Firbank et al., 2016; Haran et al., 2025; McGuinness et al., 2010).

Issues relating to language are also present along the disease continuum, typically starting with word-finding difficulties, which can be detected at MCI but are more evident during latest stages of disease (Mueller et al., 2018; Yeung et al., 2021), associated with the fusiform gyrus (Pravatà et al., 2016) and other temporal regions (Leyton et al., 2017). The impairment on most linguistic abilities, predominantly speech tasks, comprehension of complex sentences, reading and writing, are normally evident at moderate and severe stages of disease (Ortiz et al., 2021), and predominantly associated with atrophy in temporo-parietal areas (Rodríguez-Ferreiro et al., 2014). Language impairments are closely interlinked with semantic memory (Reilly et al., 2011), which, as seen above, are thought to be among the first cognitive functions affected. Non-amnestic, marked language impairment might be an indication of one atypical AD variant called “logopenic progressive aphasia” (Bergeron et al., 2018), characterised by prominent difficulties with word-generation, sentence repetition and complex comprehension, the presence of phonemic errors and paraphasia, and speech anomalies such as filler words and circumlocutions (Polsinelli & Apostolova, 2022), associated with early temporo-parietal atrophy (Whitwell et al., 2022).

In addition to spatial and visual memory, and spatiotemporal orientation, explained above, visuospatial function (both perceptual and constructional) can be impaired in AD, from earlier to latest stages of disease, linked to atrophy in occipito-parietal structures (Cronin-Golomb, 2011; Mandal et al., 2012; Salimi et al., 2018). A profile of AD characterised by predominant visuospatial impairment is defined as “posterior cortical atrophy” (Crutch et al., 2017), characterised by earlier disease onset (Yong et

al., 2023), with initial relative preservation of most cognitive domains other than visuospatial (Polsinelli & Apostolova, 2022), faster disease progression (Whitwell et al., 2022), and posterior-predominant atrophy with specific patterns and corresponding clinical features based on the localised variants (Polsinelli & Apostolova, 2022). Core features are based on the neural localisation of atrophy: the dorsal variant includes difficulty with space and object perception, simultanagnosia, optic ataxia, and oculomotor apraxia (Balint syndrome, associated with bilateral atrophy of the superior parietal lobule) or dyscalculia, dysgraphia, left–right confusion, and finger agnosia (Gerstmann syndrome, associated with the left angular gyrus), or again constructional, dressing, or limb apraxia; the ventral variant characterised by prosopagnosia (inability to recognise faces) environmental agnosia and alexia; the caudal (associated with primary visual cortex), by visual field defects and diminished visual acuity (Graff-Radford et al., 2021; Polsinelli & Apostolova, 2022).

Lastly, most people in later stages of disease tend to present with a progressive apraxia, a cognitive motor disorder that entails the loss or impairment of the ability to program motor systems to perform purposeful skilled movements (Chandra et al., 2015; Mandell & Green, 2011). Apraxia occurs frequently in AD and it is associated with disease severity, affecting the independent functioning and communication, resulting in impaired activities of daily living (Vakkila & Jehkonen, 2023). As seen above, it is also associated with the variant of posterior cortical atrophy, as well as the “motor variant”, defined by akinetic-rigid syndrome, limb apraxia, and cognitive impairment (Mathew et al., 2012), with a neuropsychological profile characterised by language, visuospatial and executive impairments and frontoparietal neurodegeneration (Polsinelli & Apostolova, 2022).

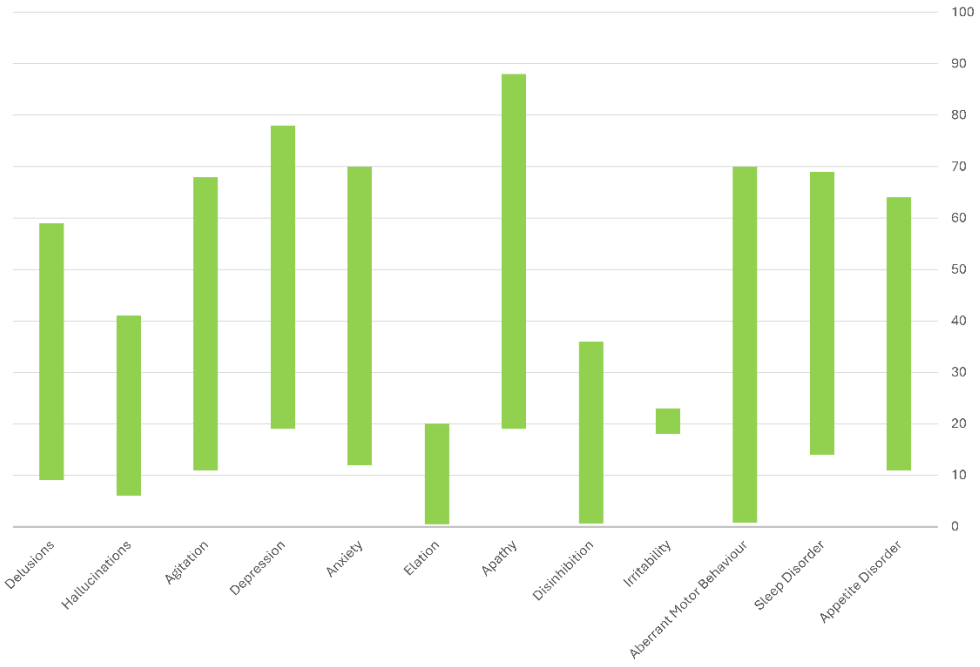
1.3. Prevalence and phenomenology of neuropsychiatric symptoms: assessment, clinical manifestation and impact on disease trajectory

Neuropsychiatric symptoms (NPS) are psychiatric and behavioural manifestations that occur in people with Alzheimer’s disease (AD) and other neurological disorders. Their cumulative prevalence over time in people with dementia has been estimated at 97% (Steinberg et al., 2008), and as seen in previous sections, they can present at prodromal and preclinical stages of disease (Gallagher et al., 2017; Ismail et al., 2016; Wise et al., 2019) with a typical, albeit variable, increasing trend over the course of disease (Borsje

et al., 2015). Although their classification varies across studies and according to the assessment tool employed (as explained in the next section, 1.3.1), neuropsychiatric symptoms are typically identified as delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behaviour, sleep disorders, and appetite/eating disorders (Cummings et al., 1994). These typically have a fluctuating presentation, both between and within individuals, with tendencies to cluster at different stages of the AD continuum (Gottesman & Stern, 2019). The individual symptoms' estimated prevalence is shown in Figure 1.2, based on the data of the most recent meta-analysis available (Zhao et al., 2016), although it is believed that with current incorporation of consistent investigation at earlier stages of disease (Gottesman & Stern, 2019; Rose et al., 2025) these estimated values might have seen an increase over the last decade.

Figure 1.2

Estimated prevalence of neuropsychiatric symptoms



Notes. The bars represent the ranges of raw prevalences (in percentage) identified across the studies in Zhao et al. (2016) (the image was adapted from Zhao et al., 2016, reproduced with permission from Elsevier, licence agreement number 6217240643684).

Alongside their near-universality, neuropsychiatric symptoms tend to be associated with serious disabling effects, such as poorer cognitive and functional outcomes (Blasutto et al., 2025; Ismail et al., 2021; You et al., 2015), earlier institutionalisation (Toot et al., 2017), accelerated disease advancement and higher rate of progression to dementia (Banks et al., 2014; Geda et al., 2014; Ismail et al., 2021; Mallo et al., 2020), higher AD biomarkers (Ronat et al., 2024), more severe dementia (Liew, 2020) and increased mortality (Peters et al., 2015), as well as greater caregiver distress (Cheng, 2017; Isik et al., 2019). For these reasons, they are considered an important target for investigations to identify their underlying mechanisms (Rosenberg et al., 2015) and find effective treatment strategies (Geda et al., 2013; Poirier et al., 2017). In fact, despite their clinical significance, NPS tend to be less consistently diagnosed with respect to the cognitive symptoms, and as a consequence undertreated (Rose et al., 2025). Among all NPS, those that are more closely linked to the adverse outcomes described above tend to be agitation, depression, anxiety and psychotic symptoms (Liew, 2020; Peters et al., 2015; Ronat et al., 2024; Toot et al., 2017).

In the past, NPS were not considered as core symptoms of AD dementia (Ferreira et al., 2024), despite them being known hallmarks of the pathology since the first recognized case of AD by Alois Alzheimer in 1907 (Geda et al., 2013). Likely due to their heterogeneity of presentation, they were not systematically characterised until relatively recent years (Cummings et al., 1994). Furthermore, NPS have been studied either as individual symptoms or clusters of symptoms. In their clinical presentation, in fact, NPS tend to overlap and be highly inter-related (Goodwin et al., 2023), which contributes to the challenge of their diagnosis (Geda et al., 2013). Based on this premise, efforts have been made to identify sub-syndromes which, based on large scale studies performed at the beginning of this century, have been typically defined by psychosis (consisting of delusions and/or hallucinations), hyperactivity (agitation, aggression, disinhibition, irritability, aberrant motor behaviour, elation/euphoria) and affective symptoms (depression, anxiety) (Aalten, Verhey, et al., 2007; Lyketsos, 2000); other symptoms, such as apathy, and sleep and appetite disorders tend to cluster more variably (Hiu et al., 2022). To further understand clustering amongst NPS, chapter 2 presents the findings of an analysis performed on a large sample of people with MCI and AD dementia, aimed at identifying the patterns of clustering of the twelve neuropsychiatric symptoms classified by Cummings et al. (1994), and explore the degree of stability of

those clusters over time. This represent an important novelty (Hiu et al., 2022), as this study adds the element of exploring the degree of stability of the clusters over time, which was not previously reported over extended period of time. In fact, considering the complexity of symptoms based on disease progression, having a sound theoretical base of how neuropsychiatric manifestations tend to co-occur, and how the patterns change over time, has important implications to achieve an increased understanding of their etiopathology and eventually, more accurate approach to the management options (Hiu et al., 2022).

On the other hand, an approach based on the study of individual symptoms, and even specific clinical manifestations of those symptoms, is helpful to clarify the underlying mechanisms, from the study of risk factors (Apostolova et al., 2014) to the study of the neuroanatomical (Rosenberg et al., 2015), cognitive (Ronat et al., 2024) and functional (Zhang et al., 2022) correlates, and their impact on the disease (Gottesman & Stern, 2019) and trajectory over time (Borsje et al., 2015; De Vito, Calamia, Weitzner, Bernstein, et al., 2018; Defrancesco et al., 2020; Ferreira et al., 2024).

1.3.1. Assessment of neuropsychiatric symptoms

With regard to the developing of assessment scales for neuropsychiatric symptoms, this has initially focused on dementia and has then been adapted to be used at the prodromal (MCI) stage. Only recently, with the emergence of compelling research on the presence of NPS at preclinical stages, a novel checklist has been proposed to detect Mild Behavioural Impairment (Ismail et al., 2017), as previously discussed. The main classical instruments, as well as the new Mild Behavioural Impairment Checklist, are introduced below, prioritising those that assess all or most neuropsychiatric symptoms, with only mentions of the most popular ones among those that are symptom specific. Most of these assessment tools are administered to a caregiver of the person with MCI or dementia, as neuropsychiatric symptoms tend to be associated with reduced insight or anosognosia (unawareness of disease) (Krejčí et al., 2026).

First of all, with the specific goal of detecting neuropsychiatric and behavioural symptomology at the preclinical and prodromal stages, the Mild Behavioural Checklist (MBI-C) has been proposed by Ismail et al. (2017). Based on the MBI criteria seen above, the MBI-C is based on the five domains shown in section 1.2.2., further divided into a

total of 34 items. These were translated from the initial domain definitions by a team of clinicians and experts in the field, to be more relevant for the administration to caregivers as follows: decreased motivation was described as a loss of “interest, motivation and drive”; emotional dysregulation as “mood or anxiety symptoms”; impulse dyscontrol as a loss of “the ability to delay gratification and control behaviour, impulses, oral intake and/or changes in reward”; social inappropriateness as “not following societal norms and/or lack of social graces, tact or empathy”; abnormal perception or thought content was described as developing “strongly held beliefs and sensory experiences”. Symptom presence (yes/no) and severity (on a scale of 1-mild, 2-moderate, or 3-severe) is assessed, based on the criteria that symptom is persistent for at least 6 months, and constitutes an impactful change from baseline behaviour.

Focusing on dementia, the most used instrument since its development by Cummings et al. in 1994 is the Neuropsychiatric Inventory (NPI), initially thought to be applied to the study of NPS at clinical stages of disease but appropriate to be used in MCI as well. This is a well-validated, reliable (Saari et al., 2022), multi-item instrument based on caregiver interview, aimed at evaluating the twelve neuropsychiatric features introduced above (although a version is available without sleep and appetite disorders, NPI-10, the most used version is the NPI-12). It is a retrospective, informant-based rating scale, within which the interviewer poses a screening question for each symptom to assess behaviours that have appeared or changed since the onset of illness and have occurred over a defined period of time (typically the previous month). The scoring system of the NPI allows coding of the presence of the symptom, as well as the frequency (on a scale of 1 to 4, 1 corresponds to Occasionally, 2 to Often, 3 to Frequently, 4 to Very frequently), severity (1 to 3, 1 corresponds to Mild, 2 to Moderate and 3 to Marked), and total score, which is the product of the two measures (1 to 12). Additionally, it collects information on the associated caregiver distress (on a scale of 0 to 5). Importantly, for each symptom, subtypes or specific manifestations of that symptom are investigated in greater depth if the caregiver answers positively to the screening questions. The NPI was used in the majority of the studies of this thesis to identify participants presenting with psychotic symptoms (in chapters 2, 4, 6 and 7).

In addition to the Interview, the NPI has also been developed as a brief questionnaire (NPI-Q) (Kaufer et al., 2000), which can be completed by the caregiver: this presents with

the same twelve neuropsychiatric symptoms, however it does not include sub-questions, only the main twelve items. In addition to the presence, it records measures of severity and caregiver distress with the same ranges used for the NPI.

While the NPI has been specifically developed to capture neuropsychiatric symptoms, other assessment tools have been proposed as an addition to existing cognitive scales, to include behavioural symptomology. An example of this is the Behavioural Rating Scale for Dementia from the Consortium to Establish a Registry for Alzheimer's Disease (BRSD CERAD) (Mirra et al., 1991; Morris et al., 1989; Tariot et al., 1995). Similarly to the NPI, it is based on a caregiver interview, assessing the presence of the behavioural symptoms over the past month. The domains of NPS identified are depressive features, psychotic features, defective self-regulation, irritability/agitation, vegetative features, apathy, aggression, and affective lability.

A few clinical rating instruments exist that assess many, but not all, NPS. One example is the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). In fact, it includes delusions (distinguishing between paranoid and other), hallucinations (coded per sensory modality), activity disturbances (wandering, abulia and inappropriate activity), aggressiveness, diurnal rhythm disturbances, affective disturbances and anxieties and phobias. Each symptom is scored from 0 to 3 based on their severity.

Similarly, the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD) (Devanand et al., 1992) assesses a smaller number of symptoms, i.e., delusions, hallucinations, illusions, behavioural disturbances and depression.

Among the assessments that specifically focus on one neuropsychiatric symptom, one of the most widely used is the Geriatric Depression Scale (GDS) (Yesavage & Sheikh, 1986). The GDS is a self-report scale designed to identify symptoms of depression in the elderly; it is highly sensitive and specific (Pocklington et al., 2016). The scale consists of 15 “YES or NO” questions, based on how the participant felt over the past week, with 6 positive answers identified as a cutoff for the presence of depression. Another instrument to assess a single symptom is the Apathy Evaluation Scale (AES) (Marin et al., 1991), which comprises 18 core items that assess and quantify the affective, behavioural, and cognitive domains of apathy with good validity and reliability (Clarke et

al., 2011). The Launay-Slade rating scale (Launay & Slade, 1981), a 12-item questionnaire scale, measures hallucinatory predisposition.

In addition to the use of assessment tools, diagnosis of neuropsychiatric symptoms has also been made on the basis of clinical criteria for specific symptoms or syndromes, for example based on the DSM (American Psychiatric Association, 1980, 1987, 1994, 2000, 2013). Many other tools and diagnostic methods have been applied through the years (see, for example, Boublay et al. (2016); Chen et al. (2021); David et al. (2010)), however here the excursus was limited to the most commonly used in recent years.

The last study presented in this thesis in chapter 8 began from an investigation of the available assessment methods, in an effort to overcome their limitations; these mainly include referring generally to a specific time period (therefore potentially missing important information based on symptom fluctuation over time) and relying on caregivers recollections of symptom presentation over an extended period of time (which may be subject to bias) (D'Antonio et al., 2022). A novel digital tool is proposed, as it is further introduced in section 1.5 of this chapter, aimed at the daily monitoring of neuropsychiatric and behavioural symptoms in dementia.

1.3.2. Neuroanatomical and cognitive correlates of neuropsychiatric symptoms

As described above, the presence of neuropsychiatric symptoms has been linked to a faster cognitive decline (Wise et al., 2019), greater cognitive impairment when present at preclinical and prodromal stages (Blasutto et al., 2025) and greater AD-related biomarker abnormality (Ronat et al., 2024). One key question which requires additional clarity relates to the factors that predispose people to the development of these symptoms. This is likely to derive from a complex combination of genetic, neurobiological and neuroanatomical features, cognitive markers and personality traits, as well as aspects relating to the environment and the interpersonal relationships, particularly with the main caregivers (Kolanowski et al., 2017; Rose et al., 2025). In order to clarify their underlying mechanisms, a large body of literature over the past few decades, and particularly since the development of the Neuropsychiatric Inventory which has greatly facilitated their diagnosis, has focused on investigating the correlates of NPS particularly with respect to affected brain areas and cognitive functions.

In Table 1.1 an overview is presented of the manifestation of NPS and the main cognitive domains and brain areas associated with these. This approach has been extensively explored in chapters 3 to 7 of this thesis, however applied to the specific study of psychotic symptoms, which are the main focus of this thesis. Chapters 3 and 5 present two systematic reviews, the first on the neuroanatomical and the second on the cognitive correlates and predictors of psychotic symptoms (the reviews presented in Table 1.1, as well as other existing systematic and narrative review were considered limited in scope with respect to the specific study of psychotic symptoms, as it is further explained in the relevant chapters). Chapters 4 and 6 discuss two independent studies derived from the findings of the systematic reviews, respectively investigating the role of regional atrophy (using MRI data, comparing the results of two approaches, whole-brain and Region of Interest) in the manifestation of psychotic symptoms, and the associations between psychotic symptoms and cognitive functions. Lastly, chapter 7 proposes a multimodal analysis, in which the predictive, combinatorial value of neuroanatomical, cognitive and neuropsychiatric variables is investigated using a machine learning method (Random Forest Analysis).

Table 1.1

Definitions and most commonly identified neuroanatomical and cognitive correlates of neuropsychiatric symptoms in AD

Symptoms	Definition	Brain areas	Cognitive functions
Delusions	False beliefs that are not amenable to change in light of clear conflictive evidence	Right frontotemporal lobe, anterior cingulate cortex and insula	Executive function, memory, attention
Hallucinations	Perceptions related to the senses, occurring in the absence of external stimuli (e.g., seeing things or hearing voices that are not there)	Anterior-posterior neural network, insula	Memory, attention, visuospatial function
Agitation	Refusal to cooperate, aggression not justified by an external cause	Frontal lobe, insula anterior and posterior cingulate cortex, amygdala, hippocampus	Executive function, visuospatial function
Depression	Depressed mood or loss of interest in pleasure and activity that is consistently and persistently present	Frontal and subcortical limbic circuits (mainly inclusive of hippocampus, amygdala, locus coeruleus, substantia nigra, and hypothalamus)	Memory, executive function, language
Anxiety	A condition characterized by excessive worry, apprehension, or fear, often accompanied by physical symptoms (e.g., restlessness, muscle tension)	Amygdala, locus coeruleus, hypothalamus, anterior mid-cingulate cortex	Executive function, attention
Elation	An elevated state of mood and happiness that does not reflect the reality of the situation	-	-
Apathy	A loss of motivation that is accompanied by diminished self-initiated behaviour, reduced goal-directed cognitive activity, and diminished emotion	Frontal cortex, anterior and posterior cingulate cortex, orbitofrontal and inferior temporal cortex	Executive function (initiation, goal setting)

Symptoms	Definition	Brain areas	Cognitive functions
Disinhibition	Acting impulsively, saying things or behaving out of context (e.g., talking to or hugging strangers), saying hurtful things	Frontal lobe, insula and anterior cingulate cortex	Executive function
Irritability	An emotional state characterized by a tendency to experience negative affective states (e.g., anger, annoyance, and frustration)	Insula, anterior cingulate cortex	Executive function
Aberrant Motor Behaviour	Presence of repetitive movements, wandering, restlessness, and pacing	Amygdala, striatum, orbitofrontal cortex and frontotemporal lobes	Executive function, language
Sleep Disorder	Excessive sleepiness during the day and insomnia with difficulty falling asleep and staying asleep, frequent awakenings during the night and premature morning awakenings	Anterior cingulate and orbitofrontal cortex	Memory, attention
Appetite Disorder	Loss or increase of appetite, change in eating habits	Anterior cingulate, orbitofrontal and medial temporal cortex, amygdala	Executive function

Notes. Symptoms definitions were derived from Cummings et al. (1994), Ismail et al. (2017) and the DSM (American Psychiatric Association, 2013); data on the most commonly identified correlates was extracted from three recent reviews, Chen et al. (2021), Chatzikostopoulos et al. (2025), and Rosenberg et al. (2015). Not enough studies were carried out on the symptom of elation to be able to draw conclusions on their correlates, likely due to their relatively low prevalence.

1.4. Definition, prevalence and theoretical frameworks of psychotic symptoms in AD

As introduced in the previous section, among neuropsychiatric symptoms, which are further explored and discussed in chapter 2, the main focus of investigation of this thesis is on psychotic symptoms, i.e. delusions and hallucinations. Chapters 3 to 7 focus on clarifying the underlying mechanisms of psychotic symptoms from different perspectives (as outlined above in section 1.3.2.). Lastly, chapter 8 presents a monitoring tool primarily focused on delusions and hallucinations, however other NPS are monitored as well. In this section, psychotic symptoms are introduced, discussing theoretical frameworks, their definition and newly proposed phenomenology-based criteria.

Among neuropsychiatric manifestations, the presence of psychotic symptoms has been particularly associated with an aggravation of the clinical picture of AD: unique associations have been in fact identified with a more rapid cognitive (Almeida et al., 2024; Köhler et al., 2013; Wilson et al., 2000) and functional decline (Bertrand et al., 2017; Fischer et al., 2012), and increased mortality (Almeida et al., 2024; Scarmeas et al., 2005); they are among the symptoms to cause greater distress for people with AD and their caregivers, resulting in a higher rate of hospitalisation (Fischer et al., 2009); lastly, when identified at the stages of Mild Cognitive Impairment (Liew, 2019) or Mild Behavioural Impairment (Yoon et al., 2022) they have been associated with an increased risk of conversion to AD (Yokoi et al., 2019).

Psychotic symptoms in AD manifest differently than they do in other syndromes such as schizophrenia. Delusions are primarily concrete and based on similar re-occurring themes, rather than being bizarre and complex; hallucinations are mainly visual rather than mainly auditory (Ballard, 2024).

Delusions are defined as fixed beliefs that are not amenable to change, even in light of conflicting evidence (American Psychiatric Association, 2013). The themes, which as mentioned above tend to be concrete and based on re-occurring themes (Fischer & Sweet, 2016), include theft, persecution, infidelity, jealousy, abandonment, and misidentification phenomena such as the belief that deceased individuals (typically parents or siblings) are still alive, not recognising one's home, spouse or family, Capgras

syndrome, and phantom boarder syndrome (Ballard et al., 2020; Koppel et al., 2014; Murray et al., 2014).

Hallucinations are perceptions occurring in the absence of corresponding external or somatic stimuli (Arciniegas, 2015); while they can reflect all senses, in AD the most common type is visual, followed by auditory, with rare reports of somatic, olfactory, and tactile experiences (El Haj et al., 2017).

Concerning their prevalence, this has proven difficult to determine, particularly due to their variability along the AD continuum (Chen et al., 2021) and the different approaches employed for their classification (Zhao et al., 2016). As seen above, in a recent systematic review and meta-analysis (Zhao et al., 2016) performed across thirty-four studies for delusions, and thirty-one for hallucinations, a substantial degree of variability was found, with delusions ranging from 9 to 59% (pooled at 31%) and hallucinations ranging from 6 to 41% (pooled at 16%); this variability across studies was only partially explained by factors considered in the review, such as age and duration of disease, therefore other factors that have yet to be determined might contribute to this. As the research into Mild Behavioural Impairment has suggested, psychotic symptoms may occur prior to prodromal and dementia stages (Ballard et al., 2020): this has constituted a problem in the past based on the exclusion in research trials of people presenting with psychotic symptoms prior to dementia. While it is important to consider the pre-existing longstanding functional psychoses through adult life, based on the different phenomenology of psychosis as it manifests in AD compared to other syndromes as discussed above, newly proposed ISTAART (Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment) and IPA (International Psychogeriatric Association) criteria reflect on the importance of their consideration prior to the onset of other clinical symptoms (Cummings et al., 2020; Fischer, 2020).

In fact, these recently revised criteria to define psychotic symptoms in AD propose that these might manifest at the stage of Mild Cognitive Impairment (Cummings et al., 2020), including pre-clinical cases in which psychotic symptoms might manifest earlier than other symptoms of cognitive decline (Fischer, 2020). With respect to their phenomenology, the IPA framework (Cummings et al., 2020) proposes that delusions and hallucinations should be treated separately, and the ISTAART criteria (Fischer, 2020)

further suggest that delusions should be considered with respect to their subtypes based on the themes of paranoia and misidentification (see section below), while hallucinations should be considered on the basis of their sensory modality.

With regard to the issue identified above of investigating neuropsychiatric symptoms as individual symptoms or within a cluster, psychotic symptoms are among the most stably identified clusters (Apostolova et al., 2014; Hiu et al., 2022) therefore both approaches have been considered across the literature and within this thesis. The first approach (individual symptoms) has been most commonly employed in studies on the neuroanatomical and neurobiological correlates of each symptom (Fischer & Sweet, 2016), that attempt to shed light on whether there are different underlying mechanisms behind their manifestation. Likewise, the symptoms are often separated in studies on clinical outcomes (e.g., with the presence of hallucinations more frequently associated with increased severity of disease and mortality (Christie et al., 2012)). Another reason to divide symptoms, is that depending on disease stage (within the AD continuum), they have different rates of prevalence, with delusions typically manifesting earlier than hallucinations (Scarmeas et al., 2005; Zhao et al., 2016). The second approach (considering the symptoms together) is, alternatively, corroborated by genetic studies (DeMichele-Sweet & Sweet, 2010; Hollingworth et al., 2012), which have highlighted the heritability and familial aggregation of psychosis in AD (Shah et al., 2017). This approach has been further supported by factor analysis investigations on the neuropsychiatric manifestations of AD (Aalten, Verhey, et al., 2007; Wadsworth et al., 2012) and MCI (Van der Mussele et al., 2013), which frequently identify a single psychotic factor among the people presenting delusions and hallucinations, that is present at different stages of the disease continuum.

Recently, in addition to the study of individual symptoms or clusters, novel approaches have emerged, particularly among the studies that attempt to explain their underlying mechanisms: focusing on specific phenomenology of psychotic manifestations. One approach is that of grouping delusional subtypes in the two overarching themes of paranoia and misidentification (normally this latter group is more closely linked to the presence of hallucinations) (e.g., Reeves et al., 2015); this approach is further explained in the next section. Another is that of considering the thematic components of delusions which occur in AD considering the individual subtypes (i.e., delusion of harm, delusion

of theft, Capgras syndrome, etc., as described above) (e.g., Castelluccio et al., 2020). Lastly, one approach to the study of hallucinations proposes considering the sensory modality (typically visual vs auditory as the two most commonly presented hallucinations) (e.g., Mori et al., 2006). Despite the challenges that such approaches may encounter (particularly those that investigate each separate delusion subtype and hallucination sensory modality may present difficulties in relation to sample size availability), they appear promising in the effort of distinguishing specific correlates of phenomena that may have distinct processes, particularly from a neuroanatomical and cognitive perspective.

1.4.1. Discussing a new, phenomenology-based classification

In the previous section it was discussed how newly proposed criteria for psychosis (Fischer, 2020) suggest accounting for the different thematic manifestations of these symptoms. As discussed above, this approach has the advantage of allowing for a detailed investigation of their key associations, as these tend to differ particularly with respect to the brain areas and cognitive functions affected in the presence of these symptoms.

It has been proposed that different psychosis subtypes might exist in addition to the distinction of delusions and hallucinations (Cook et al., 2003) which may reflect different patterns of severity of clinical picture (Perez-Madriñan et al., 2004). According to this framework, the subtypes in which delusions tend to manifest can be grouped in two themes: one comprises of paranoid-themed delusions, of which are part persecutory delusions of theft, harm, jealousy and abandonment; the other corresponds to phenomena of misidentification, including Capgras syndrome, phantom boarders, and other types of misidentification, and this is the subtype that more closely relates to hallucinations (Quaranta et al., 2015; Reeves et al., 2015). With regard to the inclusion of hallucinations within the misidentification subtype, two different approaches have been taken, mostly based on the goal of the investigation: in the context of defining assessment criteria (Fischer, 2020) and monitoring symptoms, delusions of misidentification and hallucinations are two separate symptoms, to be assessed independently of one another. However, in their clinical manifestations they tend to overlap (and this can be seen by observation of the clinical sample or statistically

by their clustering together as in Cook et al. (2003)) which might make it hard to distinguish them in association studies (Pearce et al., 2022).

Among the most compelling evidence for the utility of these two sub-syndromes within psychotic symptoms, not only the different cognitive and neuroanatomical correlates, but also the diverging disease severity and trajectory (Ismail et al., 2022; Pearce et al., 2022). In fact, overall, individuals presenting only with delusions relating to paranoia, without co-occurring symptoms of misidentification or hallucinations appear to present less cognitive impairment and brain atrophy compared to those presenting with a misidentification/hallucination profile (Wilkosz et al., 2006), and also to those without any psychotic symptom (Quaranta et al., 2015). Misidentifications, on the other hand, alongside hallucinations, tend to manifest more in association with a more aggravated clinical picture compared to paranoid phenomena (D'Antonio et al., 2019) and those without any psychotic symptoms (Quaranta et al., 2015).

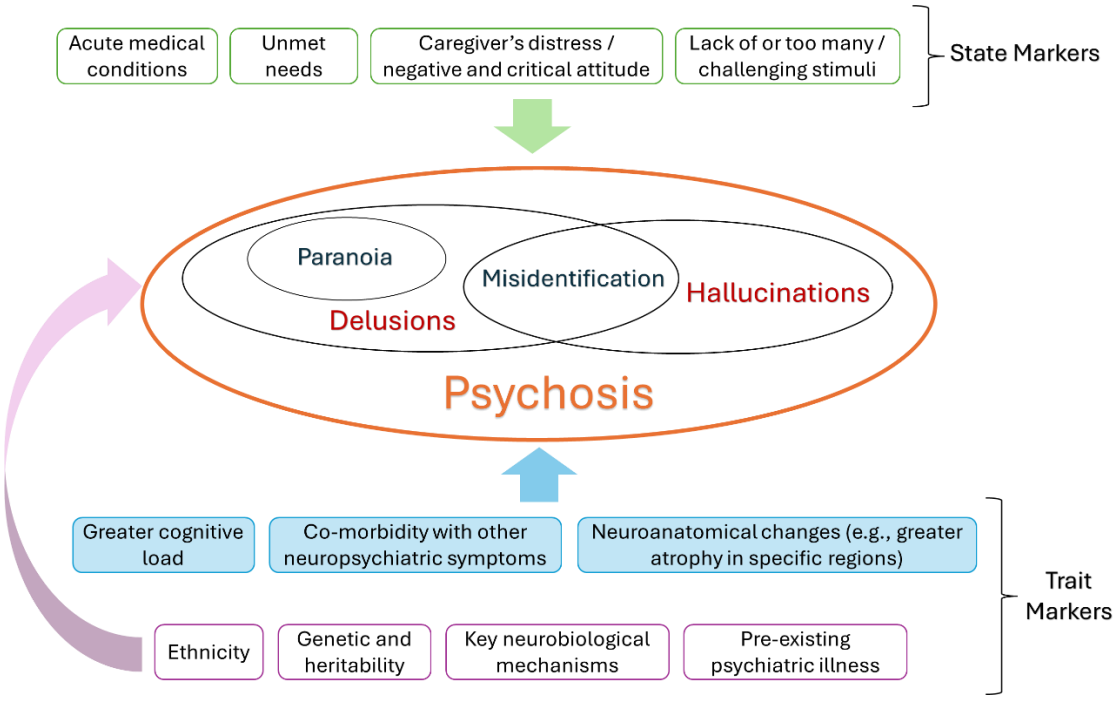
Based on these considerations, this approach has been integrated throughout the thesis, and in the data analyses contained within chapters 3 to 6, where the neuroanatomical and cognitive correlates of psychotic symptoms have been explored, specific associations are discussed with regard to the thematic approach to their classification.

1.4.2. A proposed integrated approach to the investigation of key mechanisms of psychotic symptoms

As discussed in relation to all neuropsychiatric symptoms, to understand the presence of psychosis in a proposed distinct phenotype (Fischer, 2020), it is necessary to consider the complex interaction between genetic and heritability, neurobiological and neuroanatomical, cognitive, psychiatric and psychosocial and environmental factors. El Haj et al. (2017) has proposed a model to explain the hallucinatory experience based on trait (i.e., predisposing) and state markers (contextual factors such as psychological distress or iatrogenic factors which trigger each manifestation of the symptoms). A similar approach is presented in Figure 1.3. in relation to the study of psychotic symptoms more generally.

Figure 1.3

Key mechanisms of psychotic symptoms in AD in a multifactorial model



Notes. Data for this figure was created on the basis of different studies and reviews, among which Ballard et al. (2020); Chen et al. (2021); Ismail et al. (2022); Ropacki and Jeste (2005); Shah et al. (2017) and El Haj et al. (2017). Starting from the bottom, the first two (base) levels represent key "trait markers", that may predispose to the presentation of psychotic symptoms (highlighted in blue those that are investigated in this thesis), while the top level represent potential "state markers" that may trigger these experiences.

As seen in Figure 1.3, the interaction between different factors, some intrinsic and others contextual is thought to lead to the development of psychotic symptoms in AD.

Among the pre-existing, predisposing factors (bottom level, in purple), which tend to be commonly identified in association with all psychotic symptoms, genetic and heritability factors have been proposed, with familial psychosis presentation found to be at 61% and the APOE4 (ε4) allele found to associate with psychosis (DeMichele-Sweet & Sweet, 2010; DeMichele-Sweet et al., 2021; Hollingworth et al., 2012; Shah et al., 2017). Key neurobiological mechanisms have been identified in association with psychotic symptoms (such as Dopamine D2/3 receptors, serotonin, cholinergic muscarinic

receptors, tau), which may be directly targeted in pharmacological approaches (Ballard et al., 2020). Greater vulnerability to developing psychotic symptoms has also been found in people of black ethnicity (Ropacki and Jeste, 2005) and in those presenting with pre-existing, or a history of, psychiatric disorders (Fischer & Aguera-Ortiz, 2018; Kales et al., 2015; Poulin et al., 2017).

Among the predisposing factors, neuroanatomical, cognitive and neuropsychiatric features tend to differ based on the specific psychotic phenomena (highlighted in blue in the figure). As seen in the previous section with respect to the neuroanatomical and cognitive correlates of NPS (Table 1.1), recent reviews such as Chen et al. (2021), Chatzikostopoulos et al. (2025), and Rosenberg et al. (2015) have highlighted contributions of specific brain areas such as demonstrated through right fronto-temporal atrophy, in the anterior cingulate cortex and insula in relation to delusions and fronto-occipital and insula involvement with hallucinations. While a review with a specific focus on hallucinations is not currently available, different reviews focusing on delusions e.g., Ismail et al. (2012); Reeves et al. (2012) similarly highlighted a fronto-temporal and executive involvement. With respect to cognitive functions, working memory and attention were identified in relation to both symptoms, with contributions of executive function in relation to delusions, and visuospatial function in relation to hallucinations (Chatzikostopoulos et al., 2025; Chen et al., 2021). All the above-mentioned reviews, however, also pointed out a vast degree of heterogeneity of findings across the literature with respect to these correlates, likely due to methodological differences among the studies. Furthermore, as discussed in the section on neuropsychiatric symptoms, NPS tend to overlap in their clinical manifestation: different associations have been proposed between psychotic symptoms and other NPS such as depression (Wilkosz et al., 2007; Wilkosz et al., 2006), agitation (Rafii et al., 2014), and sleep disorders (Aalten, Verhey, et al., 2007), however clear profiles are not fully understood. As mentioned above, the exploration of these factors is the key area of investigation of this thesis, explored from chapter 2 to 7 with different designs and methodological approaches.

Lastly, contextual factors (top level, green in Figure 1.3), which might trigger the manifestation of a specific symptomatic episode might include factors such medical conditions (for example, dehydration or infections); unmet needs which may arise, for

example, from feelings of fear or boredom (Kales et al., 2015); too many, or challenging stimuli (Kales et al., 2015); social isolation (El Haj et al., 2016). Importantly, a negative interaction with the main caregiver, which can be linked to caregiver distress in relation to the inability to cope with the psychotic symptomology of the person with dementia (Smith et al., 2006), has the potential to negatively impact on psychotic symptoms in a bidirectional relationship (Isik et al., 2019) and thus act as potential trigger of the symptoms. Elements of this approach have been considered in the final study of this thesis, discussed in chapter 8, that discusses the development of a digital monitoring tool, whereby alongside the monitoring of symptoms, questions were asked pertaining to any potential triggers which could be identified in the environment.

The overarching goals of this thesis are to explore the literature and propose new studies that advance the understanding of the mechanisms that might come into play to predispose certain individuals with AD to experience psychotic symptoms, and that present new approaches to their assessment. Given the detrimental impact that these symptoms have on the individuals and their caregivers, it is hypothesised that clarifying the profile of psychotic symptoms from different perspectives will contribute to informing the development of more effective assessment strategies, as proposed in chapter 8 based on the use of a novel digital tool. This is achieved through different methodological approaches, which are outlined in the next section.

1.5. Introducing the overarching methodological approaches

Within this chapter so far, the population of interest of this thesis was defined as people presenting with neuropsychiatric, and specifically psychotic symptoms in AD, at different stages of disease continuum. The main focus of this thesis has then been introduced, first as the effort to clarify the underlying mechanisms and second that of improving the assessment of psychotic and other neuropsychiatric and behavioural symptoms of AD and dementia, based on their recently understood prevalence at all stages of the AD continuum. In this section, the two main methodological approaches of this thesis are discussed, explaining their relevance within the context of neuropsychiatric and psychotic symptoms in AD, leading to the development of the rationale for the thesis's studies, and eventually the aims and objectives, set out in the next section (1.6).

1.5.1. ADNI and the importance of large datasets in association and prediction studies

ADNI, or the Alzheimer's Disease Neuroimaging Initiative (*ADNI | Alzheimer's Disease Neuroimaging Initiative*, 2026), is a public-private partnership first launched in 2004 with the overarching goal of detecting AD at the earliest possible stages, tracking the disease's progression with biomarkers, and supporting advances in AD intervention, prevention, and treatment through the application of new diagnostic methods. The wealth of data available on the ADNI database allows investigation of the relationships among the diagnostic features of AD dementia and MCI participants, as well as distinguishing among different etiopathologies for dementia, which, as seen in previous section, is an important goal within dementia research. Since its launch, data has been collected longitudinally and over the different research protocols as follows: ADNI 1 (2004-2010), ADNI GO (2009-2011), ADNI 2 (2011-2016), ADNI 3 (2016-2022), ADNI 4 (2022-present), evolving their goals and updating the neuropsychological and neuropsychiatric assessment and the availability and quality of biomarkers. The first cohort was constituted of 800 participants presenting with AD, MCI and controls with no cognitive impairment; following protocols have kept the participants enrolled in previous protocols and added respectively 200 early MCI; 150 controls, 100 MCI, 150 late MCI,150 AD; 133 elderly controls, 151 MCI, 87 AD; 200 elderly controls, 200 MCI, 100 AD. Participants enrolled to the ADNI protocols are assessed within 28 days from their recruitment: screening and baseline measures are collected alongside demographic data, and a diagnosis is made according to the NINCDS-ADRDA criteria (McKhann et al., 1984) described above, dividing the participants into four categories: suspected (probable and possible) AD, early and late mild cognitive impairment, and cognitively normal controls. Within the assessment period, participants are administered a neuropsychiatric and neuropsychological clinical battery and, if deemed fit, MRI and PET scans, alongside blood and cerebrospinal fluid collection. The same measures are collected regularly (i.e., every 6 or 12 months), through in-person and telephone visits (*ADNI 2 Protocol*, 2008; *ADNI 3 Protocol*, 2012) to monitor the participants' progression over time. ADNI provides a well-characterised dataset, and considered the large sample size of the protocols, a sufficient number of cases of psychotic symptoms was expected, to perform this thesis's analyses.

Data derived from ADNI was used in this thesis, in the studies which are presented in the chapters 2, 4, 6 and 7 (respectively studies 1, 2, 3 and 4). This introduction on the ADNI scope and wealth of data was provided to discuss the importance of using large datasets, or "Big data" (Stirland et al., 2023; Yarkoni & Westfall, 2017) in psychological models that attempt to clarify the underlying drivers and predict complex phenomena, as is the presentation of psychotic symptoms in AD. This constituted the rationale of using a secondary source of data collection for most of the studies presented in this thesis. As highlighted earlier in the introduction, complexly inter-related factors of distinct nature are likely to lead to the development of these symptoms, and as such, investigations that do not have a sufficient sample size present limitations in finding potential false positives due to overfitting (Cohen, 1962). At the same time, large datasets present the risk of allowing small effect sizes to be considered statistically significant (Stirland et al., 2023), therefore appropriate strategies for the interpretation of the findings are presented in the relevant chapters.

This thesis reports findings of two studies (chapters 4 and 6) based on a classical "association" approach using a single datatype, and one study, presented in chapter 7, which sets out to "predict" the presence of psychosis using many, multimodal predictors (Vega, 2018). This integrated approach to investigation is based on the premise that these two methods have complementary goals: single data-type association studies focus on understanding the phenomena of interest, which in this case is the presentation of different psychotic symptoms based on their neuroanatomical or neuropsychological correlates; prediction models, on the other hand, can predict the phenomena starting from high numbers of variable of different types, typically using machine learning algorithms (as set within this thesis), and they tend to generate more realistic and close to real-world associations rather than easily interpretable models (Vega, 2018; Yarkoni & Westfall, 2017). These approaches are in line with the theoretical models of psychotic symptoms introduced in section 1.4. Using a single data-type perspective allows for detailed exploration of the associations of different phenomena of psychotic symptoms, comparing the results of the findings relating to the individual symptoms of delusions and hallucinations, and the themes of paranoia and misidentification, based on the premise that each component presents different brain patterns, cognitive impairment, disease severity and trajectory (Fischer & Sweet, 2016; Pearce et al., 2022). On the other hand, a multimodal prediction model

reflects the current understanding of the nature of these symptoms, underlain by the complex combination of different types of interacting factors (Lee et al., 2024).

In both these research approaches, the use of large datasets such as ADNI is strongly encouraged as a mean for conducting analyses that are statistically meaningful; it is, however, particularly relevant in the context of machine learning, where the risk of bias due to factors such as small study size, poor handling of missing data, and failure to deal with overfitting can be high (Andaur Navarro et al., 2021). Considered the objectives which guided the studies 1 to 4 of this thesis (chapters 2, 4, 6 and 7), it was deemed preferable to rely on this secondary data approach, to conduct analyses with sufficient statistical power and generalisability (Nazir et al., 2024). The large sample size available was also useful for the project objectives (which are be further outlined below in section 1.6), to explore the division of psychotic cluster by symptom type and theme, as introduced above in paragraph 1.4.2.

On the other hand, for study 5, in chapter 8, a self-conducted recruitment with primary data collection was proposed, to explore a methodological approach based on the principles of person-centred research and co-design, as introduced in the next section.

1.5.2. The application of precision medicine and patient-involvement approaches to the study of behavioural symptoms in AD

In a distinct and complementary fashion to what described in the previous section, the last study of this thesis outlined in chapter 8 proposes a personalised approach, in which concepts deriving from precision medicine (Berkowitz et al., 2018; Isaacson et al., 2018) and person-centred (Leplege et al., 2007) care are applied to the co-design, development and trial of a monitoring tool for neuropsychiatric and behavioural symptoms of dementia, developed following the principles of active participation of stakeholders in research (Lord et al., 2022).

Earlier, within this introductory chapter, it has been shown that in order to accurately study neuropsychiatric and psychotic symptoms, a person-centred and holistic (Leplege et al., 2007) perspective is necessary. This allows for a profile of the person who is presenting with cognitive and/or behavioural symptoms that might indicate a risk for developing cognitive impairment, to be developed, on the basis of integrated data collection, starting from the person's history, to a complete neuropsychological and

neuropsychiatric assessment (McKhann et al., 1984) and, if indicated, further investigation of biological and neuroanatomical markers (Jack et al., 2024).

Such an integrated approach is also at the core of precision medicine (Berkowitz et al., 2018; Isaacson et al., 2018), which suggests taking into account individual variability in genes, environment and lifestyle to develop personalised treatment and prevention strategies. The final study of this thesis proposes to adapt these precepts to the study of individual variations over time of neuropsychiatric symptoms, by developing a tool that, given its digital nature, has the potential to monitor daily fluctuations and to capture potential triggers for symptom manifestation. This is based on the notion that the use of digital tools presents with the advantage of promoting a person-centred care approach, and supporting the individuals' involvement in their healthcare path, by allowing the users to be empowered in the understanding of the symptoms and use of the technology, and assuming an active role in the relationship with the healthcare or research professionals (Granström et al., 2020).

Based on the current knowledge on the varying level of insight of participants with AD on their experienced NPS (Krejčí et al., 2026), as seen above in section 1.3, assessment is typically done through an informant, normally an informal caregiver such as a relative or other close person. As discussed above in relation to the potential triggers of psychotic symptoms, the care of people with cognitive impairment and particularly those who present with neuropsychiatric symptoms is closely linked to an appropriate care of their main informal caregivers, as high levels of caregivers distress negatively impact on neuropsychiatric symptoms in a vicious circle (Isik et al., 2019). In fact, caregivers who feel socially isolated, unable to cope with the symptoms due to insufficient knowledge, or with overall high levels of negative emotions are more at risk of experiencing distress, with potential negative outcomes for themselves and the person with dementia (Isik et al., 2019). Based on this, the tool was designed to provide information on the symptoms in order to support clear understanding (Huang et al., 2025), and to allow space for the caregivers' reflections on the symptoms both in a qualitative manner, as well as by reporting their own levels of distress quantitatively, in addition to the collection relating to the person presenting with the symptoms.

Importantly, the tool was developed in collaboration with caregivers, to ensure that their needs and expectations on the functionality and usability would be appropriately met

(Biernetzky et al., 2025). This leads to the last theoretical basis on which this study was conducted, which is that of Public and Patient Involvement and Engagement (PPIE) in research (NHS Health Research Authority, 2026), which refers to the notion that people who have lived experience of an area of health and social care should inform and shape research in that area, research which is therefore conducted "with" the participants rather than "for" them. This has the aim to improve the quality and meaningfulness of health and social care research, by focusing on the priority outcomes of people with lived experiences. Particularly in the context of digital healthcare, this concept is fundamental not only to ensure the relevance and usefulness of the contents conceptualisation, but also of the appropriateness of the technology itself (Sohn et al., 2023), and both these aspects were applied in study 5 of this thesis.

1.6. Conclusion: gaps in the literature, rationale, aims, objectives and research questions

In this introductory chapter, the elements which form part of the thesis have been discussed in order to identify the gaps in the literature which have formed the rationale for this whole thesis project (further outlined below).

In section 1.2 a novel approach to AD diagnosis was introduced, which considers the pathological changes on a continuum where the biological hallmarks precede clinical symptoms; in this context, it has been clarified by different sets of criteria that diagnosing AD at earliest possible stages has potential to benefit the individuals, who can access new and emerging symptom management and treatment strategies. It appears evident, therefore, that a precise clinical assessment able to detect early AD symptoms is the goal to be achieved, and within the clinical assessment, the role of neuropsychiatric symptoms has been identified as a clear early marker of disease.

Section 1.3 presented an overview on neuropsychiatric symptoms, proposing different conceptualisations as cluster and individual symptoms, which still require additional clarity, and providing an overview of the main currently available assessment tools, identifying the potential for the utility of a more frequent collection of data to improve assessment in MCI and AD. Associated with greater cognitive load and neuroanatomical changes, neuropsychiatric symptoms have been identified as important treatment targets, and within these the specific focus of this thesis are psychotic symptoms,

particularly associated with negative disease outcomes overall. These were presented in section 1.4, whereby the different thematic components were introduced, highlighting the need for studies that investigate their specific associations; a holistic view of psychotic symptoms was also introduced, which has led to the rationale for building a complex model in which the value of different features in the prediction of psychosis can be studied using novel, machine learning, methods.

Lastly, in section 1.5 the overarching methodological approaches of this thesis were introduced as the complementary notions of "big data" from large international databases, used to test hypotheses based on trajectory, association and prediction, and of personalised approach to assessment, based on person-centred and precision medicine precepts, used to test the value of a novel digital tool.

The rationale for the studies which compose this thesis was therefore built on the following identified gaps in the literature: 1) there is a lack of a clear understanding of how neuropsychiatric symptoms cluster over time, and within this, how psychotic symptoms are associated with each other and with other neuropsychiatric symptoms at different stages of the AD continuum; 2) there are no available recent systematic reviews that synthesise the findings of the association studies between neuroanatomical and neuropsychological features and psychotic symptoms, resulting in a lack of clarity on the correlates, particularly in relation to the different individual symptoms; 3) novel approaches to statistics and data science, and clear analysis of psychotic sub-groups have not been consistently applied in studies that attempt to clarify the underlying mechanisms and predict psychosis from a neuroanatomical and neuropsychological perspective; 4) currently, there is no available assessment tool which allows for frequent monitoring of neuropsychiatric symptoms, and which takes into account the daily fluctuations of these symptoms, potential contextual triggers, as well as the importance of the caregivers' needs.

The main goals of this thesis were therefore to clarify the mechanisms behind the psychotic cluster of symptoms from a neuropsychiatric, neuroanatomical and neuropsychological perspective, to appraise the current instruments for assessment, proposing a novel mean for a frequent monitoring and to provide a foundation so that clinical practice may be improved in the future.

Specifically, aims of this PhD are 1) to investigate the nature of different manifestations of psychotic phenomena, by clarifying their trajectory and association with other neuropsychiatric symptoms over time, by systematically investigating previous research on their neuroanatomical and cognitive correlates and by proposing novel analyses that address the gaps identified, and 2) analyse the current assessment methods, in order to propose a novel tool which is meant to provide more accurate information, based on more frequent and person-centred based data collection.

These aims were achieved through the following objectives, research questions and hypotheses:

1) To investigate how neuropsychiatric symptoms may cluster over time, and how the clustering might be impacted by disease progression; this is achieved by carrying out a series of exploratory principal component and factor (principal axis) analyses in samples of MCI and AD dementia participants at different (up to seven) points in time. This study (study 1) is presented in chapter 2, and it addresses the research questions of a) evaluating the prevalence of psychotic and neuropsychiatric symptoms over time, and b) investigating the patterns of clustering of those symptoms to verify whether it is possible to identify relatively clear and stable syndromes.
2) To systematically investigate, and perform a coordinate-based meta-analysis (CBMA) on the neuroanatomical correlates and predictors of psychotic symptoms in AD, analysing and synthesising the findings using ad hoc comprehensive protocols for data extraction and synthesis. This systematic review and meta-analysis is presented in chapter 3, with the hypothesis that novel approaches to the synthesis of different methodological approaches to the study of brain areas will contribute to elucidating clearer associative patterns.
3) To investigate how regional atrophy (using MRI) relates to the presence of different manifestations of psychotic symptomology within a sample of people diagnosed with AD dementia and MCI by considering psychotic symptoms as a cluster, delusions and hallucinations as individual symptoms, and the thematic components of misidentification and paranoia; comparisons are also made using three different analysis techniques: Region of Interest (ROI), and the

whole-brain Voxel-based (VBM) and Surface-based morphometry (SBM). This study (study 2) is presented in chapter 4, and it addresses the research questions of a) evaluating the prevalence of each subtype of delusions and hallucinations to clarify the phenomenology and b) to investigate the regional atrophy in association with different manifestations of psychotic symptoms using different methodological approaches, based on the hypothesis that distinct patterns of regional atrophy might be associated with each manifestations.

4) To systematically investigate the relationship between psychotic symptoms and cognitive functions, by performing a systematic review which synthesises the findings using ad hoc comprehensive protocols for data extraction and synthesis. This systematic review is presented in chapter 5, and it proposes a novel approach to the synthesis of the relevance of each cognitive function in association with different manifestations of psychotic symptoms, by performing a proportion of significant associations given the total number of times each cognitive function was investigated.
5) To identify neuropsychological profiles of people who present with different groupings of psychotic symptoms (the same as in objective 3) and basing the cognitive test selection on a data-driven approach (LASSO regression) and a literature-based approach (which considers both cognitive domains, using confirmatory factor analysis-based composite scores, and specific functions using individual neuropsychological tests). This study (study 3) is presented in chapter 6, and it addresses the research question of investigating the neuropsychological profiles associated with different manifestations of psychotic symptoms, based on the hypothesis that these differ from one another when considering the thematic components.
6) To create a model which explores the combinatorial value of neuropsychiatric, neuroanatomical and neuropsychological features in predicting psychosis in AD dementia and MCI, using a machine-learning method (Random Forest Analysis). This study (study 4) is presented in chapter 7, and it addresses the research questions of a) testing the predictive ability of a model which tests the predictive value of different types of features and b) identifying the multimodal features which show greater discriminatory potential.

7) To develop, assess the feasibility, and pilot a novel digital tool, created on the basis of reviews of the phenomenology of psychotic symptoms in dementia, based on the newly proposed criteria for psychosis, and on reviews of the instruments used to assess psychotic symptoms; the digital tool is intended to optimally capture the key features of psychotic and other neuropsychiatric symptoms through daily collection, thus capturing symptom fluctuations, as well as frequency, intensity of the occurrence, and impact on both the participants with dementia and their caregivers. This study (study 5), presented in chapter 8, addresses the research questions of a) exploring the caregivers' opinions on the desired functionality and usability of a novel digital monitoring tool, b) exploring the neuropsychological profile of participants presenting with neuropsychiatric symptoms through a person-centred approach, c) assessing the performance of the tool compared with current diagnostic standard and d) exploring the value of this tool in relation to potential benefit to people with dementia and their caregivers and how that aligns with future plans to improve assessment of neuropsychiatric symptoms in clinical and research settings.

Chapter 2 – Study 1: Neuropsychiatric clusters of symptoms in Alzheimer's disease dementia and Mild Cognitive Impairment over time

This is adapted from the paper published in Current Alzheimer Research. Abbreviations and tables are adapted to be consistent with the thesis; some elements of the introduction have been deleted as they have been already amply introduced in the first chapter of the thesis.

Reference: Scarfo, S., Moshfeghi, Y., & McGeown, W. J. (2024). Assessing the Stability of Clusters of Neuropsychiatric Symptoms in Alzheimer's Disease and Mild Cognitive Impairment. Current Alzheimer Research, 21(4), 258-275. https://doi.org/http://dx.doi.org/10.2174/0115672050309014240705113444

2.1. Overview

In chapter 1, neuropsychiatric symptoms were introduced as psychiatric and behavioural manifestations that occur in people with Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), highly prevalent and associated with adverse outcome on the clinical picture, such as faster cognitive and functional decline and heightened caregiver distress. It has been highlighted that neuropsychiatric symptoms tend to highly overlap, and due to their fluctuating nature, clear patterns of association have not yet been defined over time. This study is based on this rationale, with the aim of investigating the factors that underpin neuropsychiatric symptoms and how they might evolve across several time points, in people with MCI and AD dementia (objective 1 of this thesis). In fact, while various small- and large-scale projects have investigated the underlying factors that underpin these symptoms, the identification of clear clusters is still a matter of debate. Furthermore, no study has investigated how the clusters might change across the development of AD pathology by comparing several time points as this study intends to do. Objectives of this study are to preliminarily establish the prevalence across the different time-points, and to investigate the clusters that underpin neuropsychiatric symptoms, using principal component and factor analysis, assessing how the loadings might differ based on disease stage. Data for this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database introduced in chapter 1, using scores from the Neuropsychiatric Inventory, followed up yearly from baseline until month 72 in those that had responses at that timepoint. Participant groups include those with MCI or AD dementia, or a mixture of both, presenting with at least one neuropsychiatric symptom. A series of exploratory principal component and factor

analyses (principal axis) was performed using direct oblimin rotation. The best-fitting structure was interpreted for each time point. Results of this study, presented and discussed in this chapter, indicate that a consistent unique structure cannot be identified, as the factors are unstable over time, both within the MCI and AD groups. However, some symptoms show a tendency to load on the same factors across most measurements (i.e., agitation with irritability, depression with anxiety, elation with disinhibition, delusions with hallucinations). This chapter ends by discussing the findings and potential implications: although the analyses reveal some degree of co-occurrence of neuropsychiatric symptoms across time points/samples, there is also considerable variation. In the AD group, more discrete syndromes are evident at the early time points, whereas a more complex picture of co-occurring symptoms, with differences likely reflecting disease staging, is seen at later time points. As a clear and distinctive factor structure is not consistently identified, this highlights the potential importance of sample selection (e.g., disease stage and/or heterogeneity) when studying, for example, the neurobiological underpinnings of neuropsychiatric symptoms.

2.2. Introduction

As introduced in chapter 1, the identification of neuropsychiatric sub-syndromes has been one of the main goals within the investigation on neuropsychiatric symptoms, based on the premise that in their clinical presentation, certain neuropsychiatric symptoms tend to overlap and be highly inter-related (Goodwin et al., 2023). Being able to identify clear patterns of clustering has the potential to achieve an increased understanding of their etiopathology and eventually, more accurate approach to the management options (Hiu et al., 2022).

Therefore, in the past few decades, various small and larger-scale projects have approached this issue; however, according to a recent systematic review and meta-analysis (Hiu et al., 2022), the identification of stable clusters is still unclear, and this variability likely depends on the choices of statistical and analytical approaches, the assessment tool employed, and features of the samples (such as: type(s) of dementia included, whether a particular disease stage is selected or stratification used, varying sample-sizes). A considerable degree of variability can be evident, both in terms of the

number of clusters that appear to best group the symptoms and the occurrence of each symptom in a particular cluster.

Previous work has highlighted that certain neuropsychiatric symptoms are normally found to pair together, such as delusions and hallucinations, agitation and irritability, depression and anxiety, while others, such as apathy, aberrant motor behaviour, sleep and appetite disorders present different associations (Table 2.1). Furthermore, while the most common number of factors identified across the studies was four (Aalten, Verhey, et al., 2007; Apostolova et al., 2014; Hollingworth et al., 2006; Mirakhur et al., 2004; Nagata et al., 2016), some studies propose a two (Wadsworth et al., 2012), three (Truzzi et al., 2013) or five-factor (Spalletta et al., 2010) solution.

Concerning the statistical approach, most studies have performed exploratory factor analyses or principal component analyses (PCA). While these methods appear similar, they are based on different premises: PCA aims to reduce variables into smaller numbers of components, and is therefore useful to interpret patterns of co-occurrence, however, it is not intended to identify latent constructs, which is what can be interpreted from factor analyses (Watkins, 2018). Factor analysis can be carried out with an exploratory purpose, or alternatively confirmatory factor analysis may be used, which in this field, has been guided by clinically derived constructs (e.g., Cheng et al., 2012). Both approaches have been previously used in different datasets (Hiu et al., 2022), however to the author's knowledge, a direct comparison of their findings in the same dataset has never been done.

Furthermore, while the most commonly used assessment tool is the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), introduced in chapter 1, different versions were used (Table 2.1): either its ten-item (Apostolova et al., 2014), twelve-item (Aalten, Verhey, et al., 2007; Hollingworth et al., 2006; Kang et al., 2010; Nagata et al., 2016) or shortened (NPI-Q) version (De Vito, Calamia, Weitzner, Bernstein, et al., 2018; Wadsworth et al., 2012). Importantly, few investigations specifically explore these clusters within people with MCI (e.g., De Vito, Calamia, Weitzner, Bernstein, et al., 2018) or consider the established frequency of these symptoms within MCI and how their presence at the earliest stages relates to the progression of AD pathology (Edwards et al., 2009). Further clarity on how neuropsychiatric syndromes might manifest in MCI would be useful to clarify the underlying mechanisms.

Table 2.1

Results of previous factor analytic studies using the NPI-12, NPI-10 and NPI-Q

Study	NPI Version	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Aalten et al., 2007	NPI-12	Agitation, Irritability, Disinhibition, Amb	Delusions, Hallucinations	Depression, Anxiety, Elation	Apathy	
Apostolova et al., 2014	NPI-Q	Depression, Apathy, Anxiety	Irritability, Agitation	Disinhibition, Elation, Amb	Delusions, Hallucinations	
De Vito et al., 2018 *	NPI-Q	Agitation, Elation, Apathy, Disinhibition, Irritability, Amb	Depression, Anxiety, Sleep, Appetite			
Hollingworth et al., 2006	NPI-12	Elation, Disinhibition, Amb, Sleep, Appetite	Delusions, Hallucinations	Depression, Anxiety, Apathy	Agitation, Irritability	
Mirakhur et al., 2004	NPI-12	Depression, Anxiety, Irritability, Agitation	Apathy, Amb, Sleep, Appetite	Delusions Hallucinations	Disinhibition, Elation	
Nagata et al., 2016	NPI-12	Agitation, Irritability	Apathy, Appetite	Delusions, Hallucinations	Depression, Elation, Disinhibition	
Spalletta et al., 2010	NPI-10	Agitation, Irritability, Amb	Delusions, Hallucinations	Depression, Anxiety	Elation, Disinhibition	Apathy
Truzzi et al., 2013	NPI-10	Delusions, Hallucinations, Amb	Depression, Anxiety, Agitation, Apathy	Elation, Disinhibition, Irritability		
Wadsworth et al., 2012	NPI-Q	Disinhibition, Apathy, Irritability, Agitation, Appetite, Elation, Anxiety, Depression	Delusions, Hallucinations, Sleep, Amb			

Notes. The factors of each study are ordered according to the original structure of each study. * performed analyses on MCI rather than AD dementia samples. *Abbreviations.* Amb = aberrant motor behaviour.

Lastly, in terms of stability over time, two previous studies (Bettney et al., 2012; Connors, Seeher, et al., 2018) investigated the clusters over a two-year and three-year period respectively, and they found that the clusters were not stable over time, and only in some time points they were similar to that proposed by previous research. This study proposes an investigation to span over several (up to seven) years, as one important consideration which forms the rationale for this study is that later neuropsychiatric clustering would reflect advancing disease severity and the progression of neuropathology.

Given these considerations, the aim of this study is to investigate how neuropsychiatric symptoms may cluster over time and how the clustering might be impacted by issues such as disease progression. A series of exploratory principal component and factor (principal axis) analyses will be carried out in samples of MCI and AD dementia participants, both separately and when pooled, using data made available from the large international database ADNI.

2.3. Materials and methods

2.3.1 Alzheimer's Disease Neuroimaging Initiative (ADNI)

The data was obtained from ADNI which, as introduced in chapter 1, is a public-private partnership that has the goal of detecting AD at earliest possible stages (*ADNI | Alzheimer's Disease Neuroimaging Initiative*, 2026). The wealth of data in the ADNI database enables investigation of the relationships among the diagnostic features of AD dementia and MCI at different time points, hence its suitability to address the objectives of this study. This importantly includes annual administration of the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), to allow a regular assessment of neuropsychiatric symptoms.

The present study used data from ADNI 2 and 3 protocols, specifically the NPI, in addition to the Mini Mental State Examination (MMSE) (Folstein et al., 1975), and Clinical Dementia Rating Scale (CDR) (Berg, 1988).

Within the two aforementioned protocols, the studies were conducted according to Good Clinical Practice guidelines (details on the ethical considerations can be found at *ADNI 2 Protocol* (2008) for protocol 2 and *ADNI 3 Protocol* (2012) for protocol 3). Written informed consent for the study was obtained from all participants and/or authorized

representatives, who consented to all data being retained and stored within the database and used by researchers who have access.

2.3.2. Participants

The participants included in this study (Table 2.2) were people who had MCI or AD dementia, selected according to ADNI's inclusion criteria. Those in the AD dementia group presented with CDR of 0.5 or 1, and MMSE between 20 and 26. MCI participants had a CDR of 0.5 and MMSE between 24 and 30. MCI participants were excluded if they later developed other syndromes (e.g., dementia with Lewy Bodies, Parkinson's disease). While the MCI samples at early time points included participants that later converted to AD dementia and who are therefore excluded from this group in analyses of later time points, the later time points, in addition to including people who later convert to AD dementia (or who have AD pathology and may still convert in the future), may potentially include an increased proportion of those with a non-AD aetiology. The selected participants had an assessment at baseline, and then annually until month 72. While some participants had data available beyond this, the sample sizes past month 72 were considered too small for these analyses. The samples were inclusive of participants that had scored positively on any of the neuropsychiatric symptoms at the time point selected for the analysis, thus participants were excluded if they did not present with any of the neuropsychiatric symptoms at that specific time point. While this procedure of participant selection maximised sample size at each time point, it meant that exactly the same set of participants may not, therefore, have featured at every time point. Although recommendations for sample size requirements in factor analyses are not unequivocal (Costello & Osborne, 2005), this study primarily aimed for the criterion of 10:1 ratio of participants-to-variables (Stevens, 2002), and therefore, groups that had more than one hundred and twenty participants. An exception was made for the AD group at 24 months, which, although having a ratio of 8.9:1, was deemed adequate by the Kaiser-Meyer-Olkin (Kaiser, 1974) and Bartlett's (Bartlett et al., 1954) test for factor analyses. For this reason, it was possible to investigate the MCI samples for the first four time points (from baseline to month 36), the AD samples from baseline to month 24, and for the last three time points, it was only possible to provide analyses based on the total (pooled) samples.

Table 2.2

Participants' descriptive statistics

Time point	Sample Size	Age, *M(SD)*	Gender	Education, *M(SD)*	MMSE, *M(SD)*
Baseline	517 total	72.19 (9.56)	Female=211 Male=306	16.02 (2.63)	26.08 (3.13)
	180 AD	74.81 (7.86)	Female=72 Male=108	15.64 (2.62)	22.90 (2.31)
	337 MCI	70.79 (10.08)	Female=139 Male=198	16.24 (2.61)	27.78 (1.96)
Month 12	443 total	73.67 (8.28)	Female=191 Male=252	15.95 (2.67)	25.42 (4.30)
	160 AD	74.88 (7.68)	Female=69 Male=91	15.75 (2.62)	21.71 (4.68)
	283 MCI	72.98 (8.53)	Female=121 Male=162	16.07 (2.70)	27.51 (2.11)
Month 24	324 total	74.01 (7.70)	Female=133 Male=191	16.01 (2.61)	25.60 (4.95)
	107 AD	74.98) (8.25	Female=42 Male=65	15.85 (2.70)	21.51 (5.14)
	217 MCI	73.54 (7.36)	Female=91 Male=126	16.09 (2.56)	27.61 (2.21)
Month 36	200 total	74.78 (7.06)	Female=83 Male=117	16.05 (7.06)	25.67 (4.76)
	62 AD*	75.64 (6.75)	Female=29 Male=33	16.17 (2.42)	21.14 (5.90)
	138 MCI	74.40 (7.17)	Female=54 Male=84	15.99 (2.58)	27.67 (2.04)
Month 48	168 total	76.09 (6.79)	Female=73 Male=95	15.84 (2.54)	24.96 (4.91)
	53 AD*	75.26 (6.35)	Female=26 Male=27	15.62 (2.55)	20.18 (5.57)
	115 MCI*	76.45 (6.96)	Female=47 Male=68	15.94 (2.53)	27.16 (2.35)
Month 60	137 total	78.23 (7.04)	Female=46 Male=91	15.77 (2.94)	24.10 (5.15)
	60 AD*	78.41 (6.57)	Female=20 Male=40	15.66 (2.73)	20.14 (5.29)
	77 MCI*	78.09 (7.39)	Female=26 Male=51	15.85 (3.09)	27.03 (2.29)
Month 72	121 total	79.65 (7.21)	Female=50 Male=71	15.65 (2.87)	23.35 (6.11)
	61 AD*	80.26 (6.90)	Female=30 Male=31	15.78 (2.70)	19.20 (5.80)
	60 MCI*	79.03 (7.46)	Female=20 Male=40	15.51 (3.03)	27.60 (2.00)

Notes. *At these time points, FA/PCA analyses for AD/MCI were not performed, due to low sample size. *Abbreviations.* M = mean, SD = standard deviation.

In addition to the main set of analyses described above, a further set of analyses applying principal component and factor analysis were performed on subsets of the sample that were followed longitudinally (Appendix A). The participants selected for these additional analyses were those who had sufficient data available at all the time points selected, for the AD samples and MCI samples (Appendix A).

Participants were included if they scored positively on at least one symptom, on at least one of the selected time points. Due to the restrictions in sample sizes that were available due to dropout, in these additional analyses within the AD sample it was only possible to analyse baseline data and month 12, while for the MCI sample it was possible to analyse from baseline up to and including month 36. In the analysis focusing on MCI, participants who had MCI were selected at baseline, and both the participants remaining with MCI and those who then developed AD were included in the analyses at each time point. These additional analyses allowed the stability of the clusters to be tested longitudinally within the same groups of participants, thus excluding the potential altering element of the substantial rate of dropout.

2.3.3. Assessment of neuropsychiatric symptoms: neuropsychiatric inventory

As introduced in chapter 1, the NPI (Cummings et al., 1994) is a well-validated, reliable, multi-item instrument based on caregiver interview, aimed at evaluating the twelve neuropsychiatric features of delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviour, sleep and appetite disorders.

The scoring system of the NPI allows coding of the presence of the symptom, as well as the frequency (on a scale of 1 to 4, 1 corresponds to Occasionally, 2 to Often, 3 to Frequently, 4 to Very frequently), severity (1 to 3, 1 corresponds to Mild, 2 to Moderate and 3 to Marked), and total score, which is the product of the two measures (1 to 12). Included in the analyses to determine the factor structure were scores of 0 (should the symptom be absent) and should the symptom be present, total scores ranging from 1 to 12 (which, due to the scoring options that are available for frequency and severity, and means of score calculation, excludes scoring options of 5, 7, 10 and 11).

2.3.4. Statistical analysis procedure

Principal component analyses (PCA) and factor analyses (using the principal axis extraction method) were performed on IBM SPSS, Version 28.0.1 (2021). PCA was employed first to explore the patterns of co-occurrence of symptoms, given that this method extracts the maximum variance from the data set for each component (Tabachnick & Fidell, 2006). Then, principal axis factor analyses (FA) were performed, in order to explore the underlying latent constructs. With respect to rotation, the stability of the factors was explored by comparing two oblique rotation methods, the direct oblimin (primarily), and promax (to confirm the stability of the clustering); compared to the more common orthogonal varimax, oblique rotation methods provide the advantage of considering correlations among the factors, as was expected in these datasets.

With respect to the interpretation procedure (Watkins, 2018) first, the structure derived by selecting Eigenvalues greater than one (Kaiser, 1960) was explored, considering the items that significantly loaded on a factor (cut-off value of 0.4) and the interpretation of the scree plots (Cattell, 1966). Subsequently, different fixed numbers of factors (two, three, four, or five) were selected, based on the interpretation of the scree plots, the total variance explained (minimum threshold set at 40% of the total variance explained by the model) and independence of factors (avoiding symptoms loading on multiple factors, and lower correlations among factors), to determine the best-fitting model at each time point.

2.4. Results

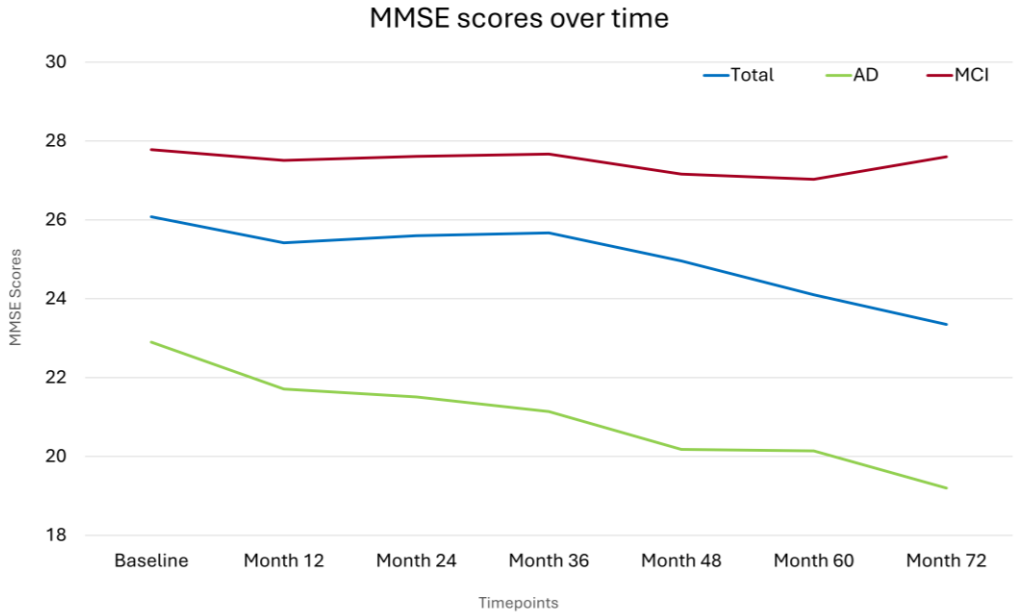
2.4.1. Descriptive statistics

The main characteristics of the samples that were analysed and the main demographic aspects such as age, gender, and education, are depicted in Table 2.2.

The mean MMSE scores are depicted in Figure 2.1, which shows the variation over time, based on group: within AD these show a decreasing trend, ranging from 22.90 at baseline to 19.20 at the last time point, which indicates progression of the disease, while in MCI group these were recorded as slightly below 28 at all the time points (i.e., they were not observed to decrease over time, probably due to the criteria applied for classification of MCI and that a person's classification would change, for example, should they decline and covert to dementia, leading to exclusion from this group).

Figure 2.1

MMSE scores on the total sample, AD dementia and MCI samples



2.4.2. Prevalence and progression of neuropsychiatric symptoms

The prevalence of neuropsychiatric symptoms (percentage of people exhibiting each symptom) according to the three samples (MCI, AD, and combined total samples) at each time point is depicted in Table 2.3 and Figure 2.2. Tables 2.4 and 2.5 depict the averages of the total NPI scores (frequency multiplied by severity) across each group (MCI, AD, and combined total samples) and illustrate how the symptoms differed in their presentation at each time point. Table 2.4 is only inclusive of participants who presented with a score of 1 or higher (in other words, those who presented with the reported symptom), while Table 2.5 is also inclusive of participants who presented with a score of 0, so this calculation includes also those people who did not have the reported symptom (and therefore reflects the impact of symptom presence, frequency and severity together).

Considering first the prevalence of each symptom within each of the samples, overall this has a slightly lower occurrence in MCI compared to AD, with the exception of sleep

disorders which consistently occurred more in MCI; furthermore, while in AD prevalence tended to increase from baseline to the following measurements, the values recorded for MCI appeared more stable.

Within the groups of participants with a diagnosis of AD, the most prevalent symptoms were apathy (45.0 - 56.9%), depression (37.7 - 54.1%) and irritability (35.8 - 48.4%), and the least prevalent symptoms were elation (ranging from 1.6 - 11.3%), hallucinations (6.7 - 18%), and delusions (10.6 - 18.1%). In terms of the neuropsychiatric symptom total scores (frequency multiplied by severity), Tables 2.4 and 2.5 show that the average total NPI scores were typically higher in AD compared to MCI.

When calculated using the total NPI scores (frequency multiplied by severity) of those who presented with each symptom of interest only (Table 2.4), fluctuations can be noted across time points, with no symptom increasing across every time point. By including in the averages also those who scored zero (who did not have the symptoms), hallucinations, depression and aberrant motor behaviour all had their highest scores at month 72 (Table 2.5).

For the MCI groups, a somewhat similar trend was observed in terms of the overall pattern of all symptoms, with slightly lower prevalences overall compared to AD: the most prevalent symptoms were irritability (ranging from 37.7 – 51.7%), depression (37.0 – 47.5%) and sleep disorder (28.3 – 40.9%), while the least prevalent symptoms, like the AD group, were hallucinations (ranging from 0 to 2.3%), delusions (0.7 - 5%), and elation (0 - 4.6%). The average total NPI scores for each symptom, as calculated using only the scores of those who had the symptoms (Table 2.4), again showed considerable fluctuation across time points, with sleep, agitation and depression having their highest scores at month 72, while apathy, disinhibition, irritability, appetite disorder, and anxiety were highest at month 60. Considering the averages of all scores, including those of zero (who did not have the symptom), irritability highest at month 72, sleep at month 48, and apathy at month 36 (Table 2.5).

Figure 2.2

Graphic representation of the trajectory of prevalence of neuropsychiatric symptoms at each time point



Table 2.3

Prevalence of neuropsychiatric symptoms at each time point

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Delusions	Total	5.2%	8.3%	7.1%	4.5%	5.4%	8.8%	11.7%
	AD	10.6%	18.1%	17.7%	12.9%	13.2%	15%	16.4%
	MCI	2.4%	1.4%	1.8%	0.7%	1.7%	3.9%	5.0%
Hallucinations	Total	3.5%	4.3%	4.6%	6.0%	3.0%	2.7%	9.1%
	AD	7.2%	8.1%	9.3%	17.7%	7.5%	6.7%	18%
	MCI	1.5%	0.7%	2.3%	0.7%	0.9%	0%	0%
Agitation	Total	29.4%	30.0%	31.5%	36.5%	33.3%	34.3%	33.1%
	AD	26.1%	34.4%	42.1%	50.0%	48.1%	36.7%	39.3%
	MCI	25.8%	26.5%	26.3%	30.4%	26.1%	32.5%	26.7%
Depression	Total	47.4%	44.1%	42.3%	40.5%	41.1%	46.0%	48.8%
	AD	47.2%	45.0%	43.9%	48.4%	37.7%	46.7%	54.1%
	MCI	47.5%	42.8%	41.5%	37.0%	40.6%	45.5%	43.3%
Anxiety	Total	28.8%	31.3%	29.9%	32.5%	30.4%	30.7%	19.0%
	AD	33.3%	40.6%	39.3%	41.9%	37.7%	35.0%	18.0%
	MCI	26.4%	35.1%	25.3%	28.3%	37.0%	27.3%	20.0%
Elation	Total	3.7%	5.1%	5.6%	4.5%	4.8%	4.4%	2.5%
	AD	4.4%	6.9%	7.5%	1.6%	11.3%	10%	1.6%
	MCI	3.3%	2.8%	4.6%	4.3%	1.7%	0%	3.3%

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Apathy	Total	45.0%	38.0%	32.1%	37.5%	30.4%	32.8%	34.7%
	AD	50.0%	56.9%	45.5%	51.6%	54.7%	45.0%	47.5%
	MCI	27.0%	26.5%	23.5%	31.2%	19.1%	33.4%	21.7%
Disinhibition	Total	18.0%	19.0%	19.1%	24.0%	23.2%	22.4%	2.04%
	AD	21.7%	21.2%	38.0%	33.9%	28.3%	26.7%	36.1%
	MCI	16.0%	16.5%	14.7%	19.6%	20.9%	19.5%	11.7%
Irritability	Total	38.4%	43.0%	41%	47.5%	41.7%	46.0%	57.9%
	AD	38.9%	42.5%	39.3%	48.4%	35.8%	41.7%	44.3%
	MCI	37.7%	42.4%	41.9%	47.1%	44.3%	49.4%	51.7%
Aberrant Motor Behaviour	Total	11.1%	14.1%	12.7%	12.0%	11.7%	18.2%	19%
	AD	17.8%	26.3%	26.2%	24.2%	18.9%	30.0%	27.9%
	MCI	5.9%	6.0%	6.0%	6.5%	7.0%	9.1%	10.0%
Sleep Disorder	Total	30.9%	32.2%	37.7%	37.5%	39.3%	36.5%	28.1%
	AD	22.8%	21.9%	31.8%	32.3%	35.8%	45.0%	27.9%
	MCI	35.3%	37.1%	40.6%	39.9%	40.9%	37.7%	28.3%
Appetite Disorder	Total	19.9%	26.0%	24.7%	22.5%	25.0%	29.9%	24.0%
	AD	28.4%	36.9%	41.1%	37.1%	42.4%	33.3%	24.6%
	MCI	14.8%	18.7%	16.6%	15.9%	16.5%	27.7%	23.3%

Table 2.4

Average scores for the neuropsychiatric symptoms at each time point

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Delusions	Total	3.5	3.6	3.6	3.4	4.7	2.5	3.2
	AD	4.1	4.2	3.1	2.8	5.8	2.7	3.7
	MCI	2.3	2.7	6.0	8.0*	1.0	1.6	2.6
Hallucinations	Total	2.1	2.0	3.2	1.7	4.0	2.5	2.7
	AD	2.0	2.8	2.5	1.5	4.7	2.5	2.7
	MCI	2.2	1.0	4.6	4.0*	1.0*	NA	NA
Agitation	Total	2.8	2.7	2.8	3.0	3.1	2.9	3.6
	AD	3.1	2.8	2.9	2.6	3.5	3.0	3.5
	MCI	2.6	2.6	2.8	3.2	2.7	2.8	3.8
Depression	Total	2.1	2.4	2.6	2.7	2.7	2.6	2.9
	AD	2.3	2.7	2.8	3.1	3.4	2.6	2.8
	MCI	2.0	2.2	2.5	2.4	2.5	2.7	2.9
Anxiety	Total	2.9	2.8	3.7	3.3	2.4	3.2	3.4
	AD	2.9	2.9	4.5	4.1	3.1	3.3	4.1
	MCI	2.9	2.8	3.0	2.7	2.7	3.1	2.7
Elation	Total	2.8	3.9	3.1	4.0	1.7	1.6	1.3
	AD	3.3	5.3	3.2	8.0*	1.5	1.6	2.0*
	MCI	2.4	3.3	3.0	3.3	2.5	NA	1.0
Apathy	Total	3.5	4.0	4.1	4.3	4.5	5.5	4.2
	AD	3.5	4.6	4.6	4.4	5.4	6.0	4.7
	MCI	3.5	3.3	3.6	4.2	3.4	4.9	3.1

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Disinhibition	Total	2.4	2.5	2.3	3.4	2.2	3.2	2.4
	AD	2.4	3.0	3.0	4.0	2.5	3.2	2.6
	MCI	2.4	2.4	1.7	2.9	2.0	3.0	1.8
Irritability	Total	2.9	3.0	3.0	3.1	3.0	3.4	3.1
	AD	3.3	3.5	3.5	3.2	4.0	3.7	3.1
	MCI	2.7	2.7	2.8	3.0	2.7	3.2	3.1
Aberrant	Total	3.4	4.3	4.2	5.1	3.8	4.2	4.8
Motor	AD	3.8	4.9	3.7	5.1	5.4	4.1	5.0
Behaviour	MCI	3.7	3.5	5.3	5.2	2.5	4.5	4.1
Sleep	Total	3.8	4.0	3.9	4.1	4.7	4.0	4.8
Disorder	AD	3.2	4.6	4.4	5.1	6.7	4.0	5.0
	MCI	4.0	3.9	3.6	3.7	3.9	3.9	4.5
Appetite	Total	4.7	4.7	5.0	4.4	5.2	5.3	5.0
Disorder	AD	4.9	5.4	5.6	5.5	5.9	5.5	5.0
	MCI	4.5	4.3	4.3	3.3	4.5	5.2	5.0

Notes. The average scores reported here were calculated from the Total NPI Scores (range 1-12) for each Neuropsychiatric Symptom for each group at each time point for those who presented with each symptom. The total NPI scores for each symptom were calculated by multiplying the frequency scores (range 1-4) and severity scores (range 1-3) and reported to 1 decimal place. *These scores do not represent averages but the score of the only participant who presented that symptom at that time point. NA: No participant presented that symptom at that time point.

Table 2.5

Average scores of neuropsychiatric symptoms at each time point including zero

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Delusions	Total	0.18	0.30	0.25	0.15	0.25	0.21	0.66
	AD	0.43	0.76	0.55	0.37	0.77	0.41	0.60
	MCI	0.05	0.03	0.11	0.05	0.01	0.06	0.13
Hallucinations	Total	0.07	0.08	0.14	0.10	0.11	0.07	0.45
	AD	0.15	0.23	0.23	0.27	0.35	0.16	0.49
	MCI	0.03	0.01	0.10	0.02	0.01	NA	NA
Agitation	Total	0.83	0.81	0.90	1.10	1.04	1.00	1.63
	AD	1.13	0.98	1.22	1.33	1.75	1.11	1.37
	MCI	0.67	0.71	0.75	0.99	0.71	0.90	1.01
Depression	Total	1.01	1.06	1.12	1.10	1.14	1.24	1.58
	AD	1.12	1.23	1.23	1.51	1.30	1.23	1.55
	MCI	0.96	0.96	1.07	0.91	1.06	1.24	1.28
Anxiety	Total	0.84	0.89	1.11	1.08	0.88	0.99	1.05
	AD	0.98	1.20	1.80	1.74	1.18	1.26	0.75
	MCI	0.76	0.72	0.77	0.78	0.74	0.85	0.55
Elation	Total	0.10	0.19	0.17	0.14	0.08	0.07	0.06
	AD	0.15	0.36	0.24	0.12	0.16	0.16	0.03
	MCI	0.08	0.09	0.13	0.14	0.04	NA	0.03

Symptom	Group	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72
Apathy	Total	1.20	1.52	1.34	1.62	1.38	1.83	2.00
	AD	1.77	2.65	2.32	2.27	2.96	2.70	2.27
	MCI	0.94	0.88	0.85	1.33	0.65	1.15	0.68
Disinhibition	Total	0.43	0.48	0.45	0.82	0.52	0.70	0.90
	AD	0.52	0.64	0.84	1.38	0.71	0.86	0.96
	MCI	0.38	0.40	0.26	0.57	0.43	0.58	0.21
Irritability	Total	1.11	1.30	1.25	1.46	1.27	1.56	1.72
	AD	1.28	1.51	1.38	1.56	1.45	1.55	1.40
	MCI	1.02	1.17	1.19	1.42	1.20	1.58	1.61
Aberrant Motor Behaviour	Total	0.38	0.60	0.53	0.62	0.44	0.78	1.48
	AD	0.67	1.30	0.97	1.24	1.01	1.25	1.40
	MCI	0.22	0.21	0.32	0.34	0.17	0.41	0.41
Sleep Disorder	Total	1.18	1.31	1.47	1.55	1.88	1.46	1.97
	AD	0.75	1.01	1.42	1.66	2.43	1.43	1.40
	MCI	1.41	1.48	1.49	1.50	1.62	1.49	1.30
Appetite Disorder	Total	0.94	1.24	1.25	1.01	1.32	1.60	1.84
	AD	1.45	1.99	2.32	2.06	2.56	1.83	1.22
	MCI	0.67	0.81	0.72	0.53	0.74	1.42	1.18

Notes. The score reported here are derived from the Total Score including the participants who scored 0, therefore reflect the severity of the symptoms at each time point within all participants (range 0-12). NA: No participant presented that symptom at that time point.

For the longitudinal analyses, that followed the same participant samples over time, for the AD group, the symptoms of greatest prevalence (Appendix A) were apathy (ranging 44.8 - 48.9%), agitation (30.6 - 31.3%), depression (38.7 - 39.4%) and irritability (34.0 - 37.4%). Those with the lowest prevalence were elation (ranging 3.4 - 4.7%) and hallucinations (6.2 - 7.4%), while the greatest increases over time were observed in delusions (8.9 increasing to 17.0%) and aberrant motor behaviour (16.3 increasing to 25.8%). The average score (frequency X severity), irrespective of whether only people with the symptoms were included in the calculations or not (Appendix A), increased across time points (baseline to month 12) for every symptom.

For the longitudinal follow-up of the group who were classified as MCI at baseline, the symptoms of greatest prevalence (Appendix A) were depression (ranging 31.0 - 33.1%), anxiety (15.2 increasing to 21.5%), irritability (25.2 increasing to 32.1%) and sleep disorder (26.3 – 28.9%); the lowest prevalence were hallucinations (1.0 increasing to 6.3%), delusions (2.1 increasing to 4.2%), and aberrant motor behaviour (2.6 increasing to 10.0%), and the greatest increase was in apathy (17.8 increasing to 29.4%). The average scores fluctuated more in the MCI group, and only apathy increased across all time points (baseline to month 36) irrespective of whether only people with the symptoms were included in the calculations or not.

2.4.3. Preliminary assumption testing

Prior to proceeding with the factor analyses, assumptions were tested using SPSS, Version 28.0.1 (2021): 1) correlation among variables (correlation matrix) did not show loadings >.80; 2) Kaiser-Meyer-Olkin and Bartlett's test for factor analyses showed the adequacy of the sample sizes.

2.4.4. Interpretation of the component/factor structures

Exploratory PCA and FA were performed on the three groups (total sample, AD, and MCI), at each time point available.

The factors/components reported in Tables 2.6, 2.7, and 2.8 reflect the best-fitting models for the total sample, AD group, and MCI group, respectively. These were interpreted by comparing the different rotation methods, based on the following considerations: 1) Eigenvalues greater than 1; 2) item loadings on the factors were greater than 0.4; 3) interpretation of the scree plot patterns; 4) minimum 40% total

variance explained by the model; 5) best achievable independence of factors (based on the following criteria: lower correlation among factors, few/no cross-loading of items on more than one factor). Figures 2.3, 2.4 and 2.5 provide a visual depiction of the factors (derived from the FA) across the time-points.

2.4.5. Results of the main analyses chosen for maximum sample size

The results of the total sample group (inclusive of AD dementia and MCI participants) are reported in Table 2.6. At baseline and month 12, the best-fitting structure according to the above criteria was with four components/factors, which accounted for more than 50% of the total variance. The symptoms loading on a component/factor were not completely consistent over the two methods, and at the two different time points, however, some pairings of symptoms emerged as: symptoms related to affect/mood (depression and anxiety); symptoms related to hyperactivity (agitation and irritability); symptoms related to impulse control and hypomania (disinhibition and elation); psychotic symptoms (delusions and hallucinations). Other symptoms related to apathy, aberrant motor behaviour, as well as neurovegetative functions (sleep and appetite disorders) tended to vary more frequently in terms of the components/factors onto which they loaded. From month 36 to 60, a three component/factor structure best described the data, explaining more than 40% of the variance, while for month 72, more than 40% of the variance and best-fitting model was obtained by two components/factors. Across these time points, the associations described above were found to a certain degree, but still with considerable variance (visually depicted in Figure 2.3).

Table 2.6

PCA and FA on the total samples at all time points

		PRINCIPAL COMPONENT ANALYSIS				FACTOR ANALYSIS			
Time point	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Baseline	55%	Depression[1] Anxiety[1] Agitation[2] Irritability[2]	Elation[3] Disinhibition[3]	Apathy[5] Sleep[5] Appetite[5]	Delusions[4] Hallucinations[4]	Agitation[2] Irritability[2]	Elation[3] Disinhibition[3]	Apathy[5]	Depression[1] Anxiety[1]
Month 12	54%	Agitation[2] Anxiety[1] Irritability[2]	Delusions[4] Hallucinations[4] Apathy[5] Amb[5]	Elation[3] Disinhibition[3]	Depression[1] Sleep[5] Appetite[5]	Delusions[4] Agitation[2] Irritability[2]	Hallucinations[4] Amb[5]	Elation[3] Disinhibition[3]	Depression[1] Anxiety[1] Apathy[5]
Month 24	44%	Delusions[4] Hallucinations[4] Agitation[2] Depression[1] Anxiety[1] Irritability[2]	Elation[3] Disinhibition[3] Sleep[5] Appetite[5]	Apathy[5] Amb[5]		Delusions[4] Hallucinations[4] Depression[1] Anxiety[1]	Agitation[2] Irritability[2] Elation[3] Disinhibition[3]	Apathy[5] Appetite[5]	
Month 36	44%	Delusions[4] Hallucinations[4] Anxiety[1] Sleep[5]	Agitation[2] Disinhibition[3] Irritability[2] Amb[5]	Depression[1] Elation[3] Apathy[5] Appetite[5]		Agitation[2] Anxiety[1] Irritability[2]	Disinhibition[3] Amb[5]	Depression[1] Apathy[5] Appetite[5]	

		PRINCIPAL COMPONENT ANALYSIS				FACTOR ANALYSIS			
Time point	**Variance**	**Component 1**	**Component 2**	**Component 3**	**Component 4**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Month 48	46%	Agitation[2] Depression[1] Anxiety[1] Elation[3] Disinhibition[3] Irritability[2]	Delusions[4] Hallucinations[4] Apathy[5] Sleep[5]	Amb[5] Appetite[5]		Agitation[2] Depression[1] Irritability[2]	Delusions[4] Apathy[5] Sleep[5]	Disinhibition[3] Amb[5]	
Month 60	47%	Agitation[2] Apathy[5] Disinhibition[3] Irritability[2]	Delusions[4] Elation[3] Appetite[5]	Hallucinations[4] Depression[1] Anxiety[1] Sleep		Agitation[2] Apathy Disinhibition[3] Irritability[2]	Delusions[4] Elation[3] Appetite[5]	Depression[1] Anxiety[1]	
Month 72	40%	Delusions[4] Hallucinations[4] Anxiety[1] Amb[5] Sleep[5] Appetite[5]	Agitation[2] Depression[1] Disinhibition[3] Irritability[2]			Delusions[4] Hallucinations[4] Anxiety[1] Amb[5] Sleep[5]	Agitation[2] Disinhibition[3] Irritability[2]		

Notes. The factors are reported as extracted using principal axis factoring extraction method, and direct oblimin rotation method; the promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, these were reported according to the direct oblimin method. 1. Symptoms related to affect/mood; 2. Symptoms related to hyperactivity; 3. Symptoms related to impulse control and hypomania; 4. Psychotic symptoms; 5. Apathy/aberrant motor behaviour/neurovegetative functions. *Abbreviations*. Amb = aberrant motor behaviour.

Table 2.7

PCA and FA on the AD samples at all time points available

		PRINCIPAL COMPONENT ANALYSIS					FACTOR ANALYSIS				
Time point	**Variance**	**C 1**	**C 2**	**C 3**	**C 4**	**C 5**	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**
Baseline	64%	Agitation Irritability	Elation Disinhibition	Delusions Hallucinations Sleep	Apathy Appetite	Depression Anxiety Amb	Depression Anxiety	Elation Disinhibition	Delusions Hallucinations Sleep	Agitation Irritability	Apathy Appetite
Month 12	48%	Delusions Agitation Depression Anxiety Irritability	Elation Disinhibition Appetite	Hallucinations Apathy Amb Sleep			Delusions Agitation Depression Anxiety Irritability	Hallucinations Apathy Amb	Elation Disinhibition		
Month 24*	54%	Delusions Hallucinations Agitation Depression Anxiety Irritability	Elation Disinhibition Sleep Appetite	Apathy Amb			Delusions Hallucinations Agitation Depression Anxiety Irritability	Elation Disinhibition Sleep	Apathy Amb		

Notes. The factors are reported as extracted using principal axis factoring extraction method, and direct oblimin rotation method; the promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the direct oblimin method. *This group had a ratio of less than 10:1 observation per variable (107 participants – 8.9:1). *Abbreviations.* Amb = aberrant motor behaviour; C = component; F = factor.

Table 2.8

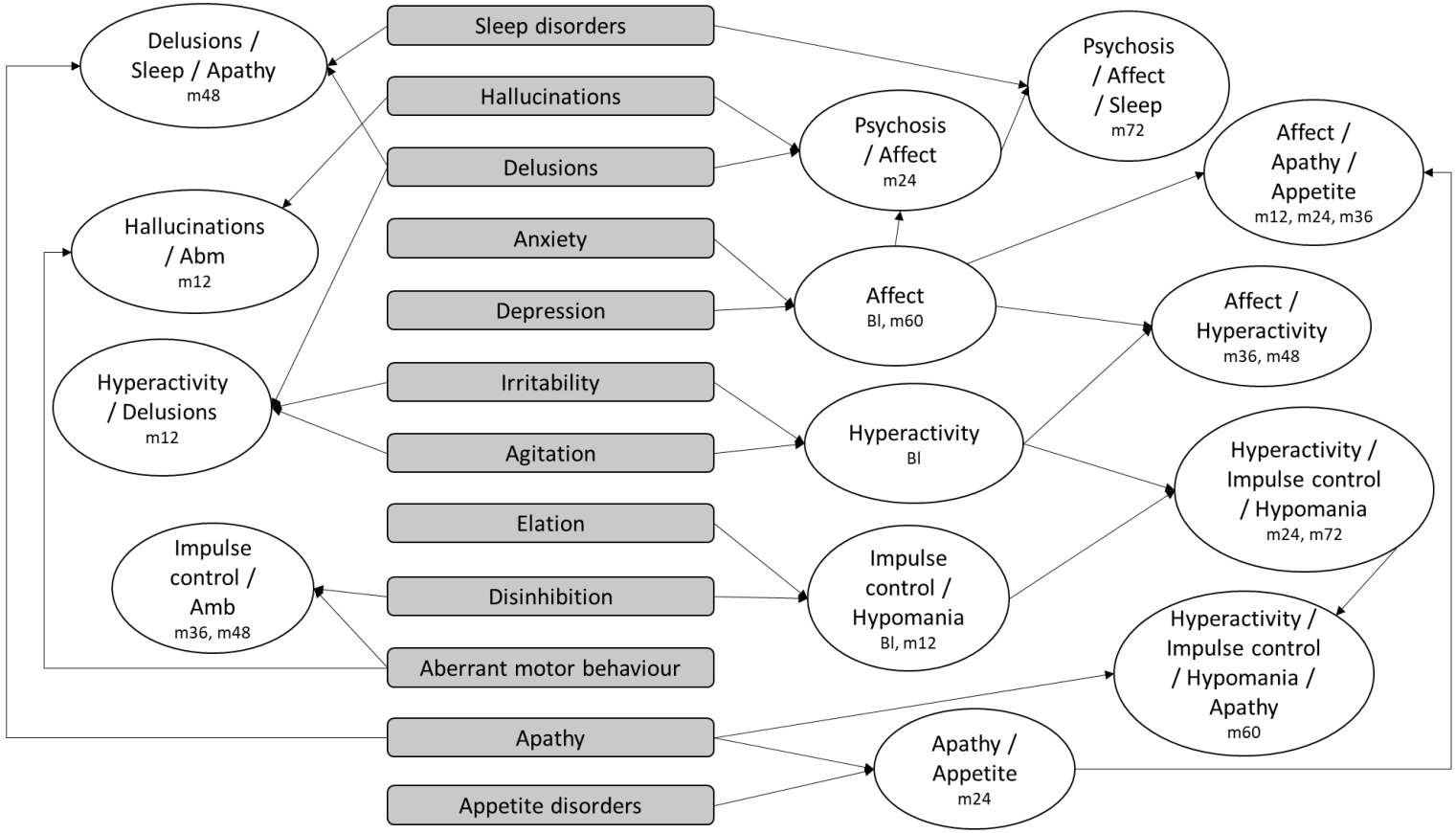
PCA and FA on the MCI samples at all time points available

		PRINCIPAL COMPONENT ANALYSIS					FACTOR ANALYSIS				
Time point	**Variance**	**C 1**	**C 2**	**C 3**	**C 4**	**C 5**	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**
Baseline	47%	Agitation Disinhibition Irritability	Delusions Depression Anxiety	Elation Apathy Amb	Sleep Appetite		Agitation Disinhibition Irritability	Delusions Depression Anxiety	Elation Apathy Amb	Sleep Appetite	
Month 12	41%	Delusions Agitation Depression Anxiety Irritability	Elation Disinhibition Appetite	Hallucinations Apathy Amb Sleep			Agitation Disinhibition Irritability	Elation	Depression Apathy		
Month 24	59%	Agitation Elation Irritability	Depression Apathy	Sleep Appetite	Delusions Hallucinations Anxiety	Disinhibition Amb	Depression Apathy	Agitation Elation Irritability	Hallucinations Anxiety	Disinhibition Amb	Sleep Appetite
Month 36	49%	Hallucinations Anxiety Irritability Sleep	Delusions Depression Apathy Appetite	Agitation Elation Disinhibition Amb			Hallucinations Anxiety Irritability Sleep	Delusions Depression Apathy	Agitation Disinhibition Amb		

Notes. The factors are reported as extracted using principal axis factoring extraction method, and direct oblimin rotation method; The promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the direct oblimin method. The order of the symptoms within each factor reflects the loading size (higher contributions to the factor are first, in descending order). *Abbreviations*. Amb = aberrant motor behaviour; C = component; F = factor.

Figure 2.3

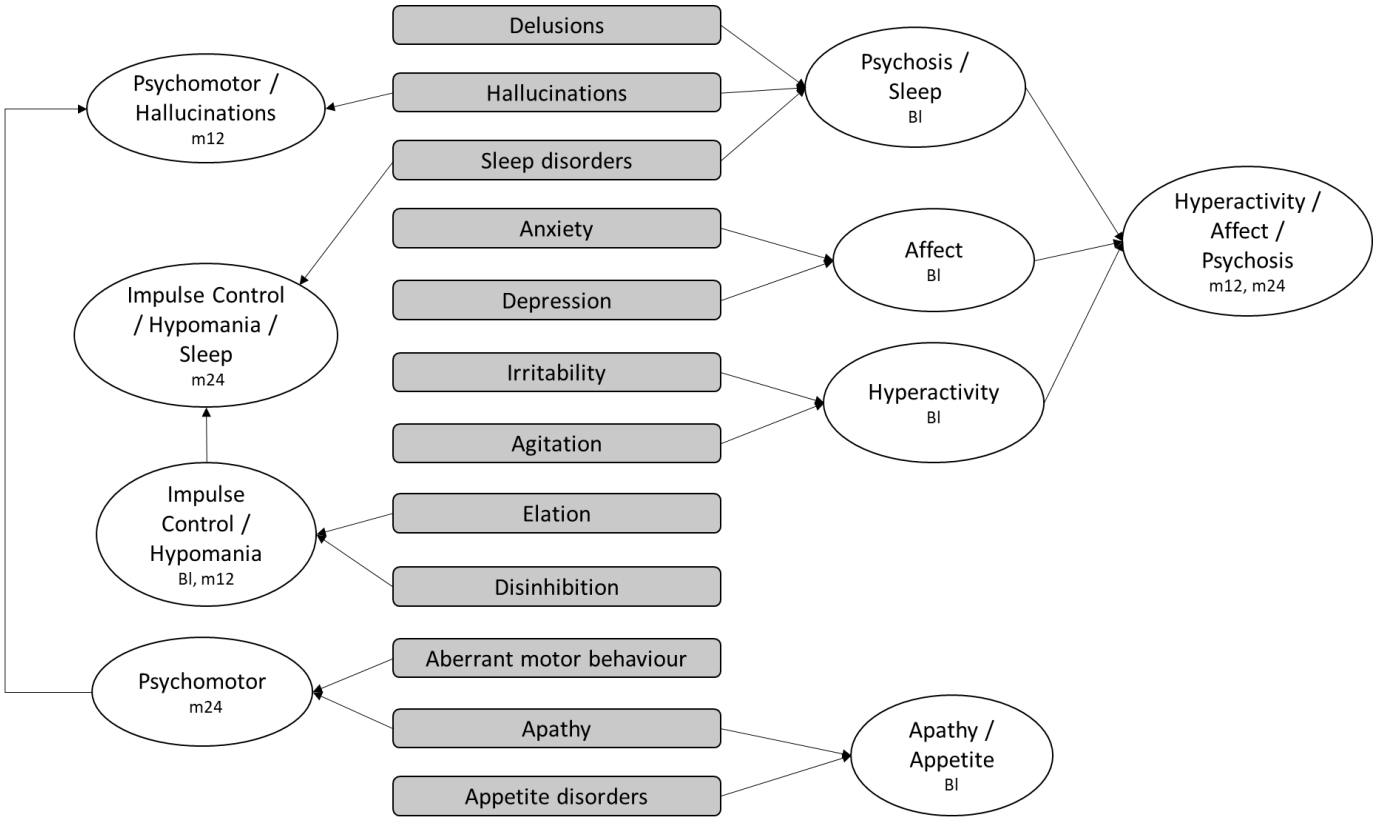
Overview of the factors resulting from the FA in the total samples



Notes. The figure shows the neuropsychiatric symptoms (rectangles) and the factors they were found to load on to (ovals) over time, showing greater complexity at latest time points. *Abbreviations*. Bl = baseline; m = month; Amb = aberrant motor behaviour.

Figure 2.4

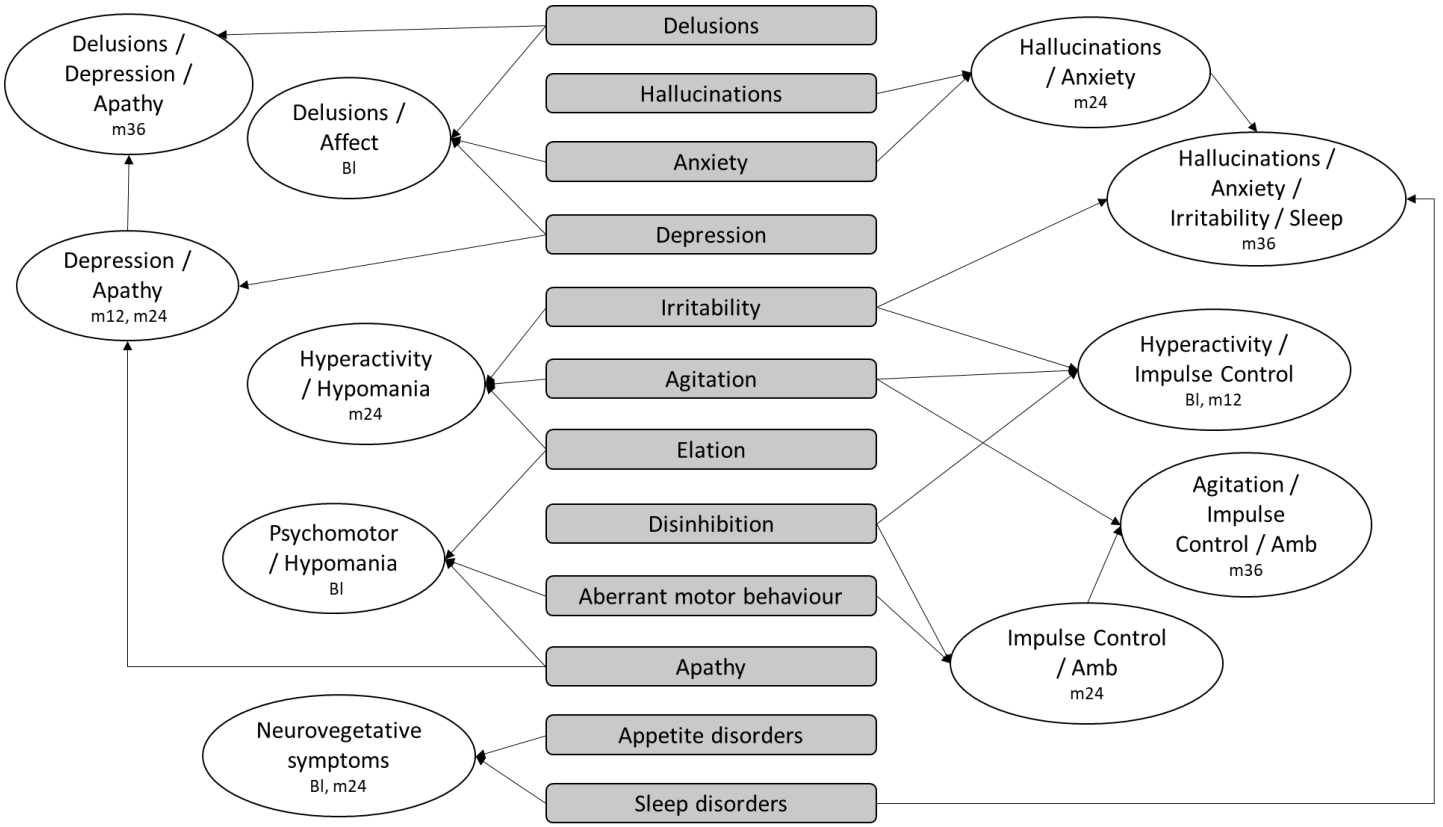
Overview of the factors resulting from the FA in the AD sub-group



Notes. The figure shows the neuropsychiatric symptoms (rectangles) and the factors they were found to load on to (ovals) at the different time points. This illustrates how at baseline, the factors reflect more defined neuropsychiatric syndromes, while with the progression of AD pathology these tend to become more complex (i.e., composed by multiple syndromes). *Abbreviations*. Bl = baseline; m = month.

Figure 2.5

Overview of the factors resulting from the FA in the MCI sub-group



Notes. The figure shows the neuropsychiatric symptoms (rectangles) and the factors they were found to load on to (ovals) at the different time points. This illustrates how within MCI, more variation was found between neuropsychiatric syndromes at the different time points, and a pattern could not be identified to explain the difference between earlier and later time points. *Abbreviations*. Bl = baseline; m = month; Amb = aberrant motor behaviour.

The results of the analyses performed considering only participants with AD dementia are reported in Table 2.7 and visually depicted in Figure 2.4. Here, five components/factors were found to better explain the model at baseline, evidencing similar dimensions as found in the total sample analyses, which can be described as affect/mood, impulse control/hypomania, psychosis (with sleep), hyperactivity, and lastly apathy with appetite. In the two subsequent time points analysed, on the other hand, a three component/factor structure fitted better, explaining 48% (month 12) and 54% (month 24) of the variance. At both time points, the first component/factor was composed of psychotic (delusions and/or hallucinations), affective (depression and anxiety), and hyperactive elements (agitation and irritability), while the other two were mainly: apathy with aberrant motor behaviour, and impulse control/hypomania-related symptoms (disinhibition and elation).

Lastly, concerning Mild Cognitive Impairment (Table 2.8 and Figure 2.5), the best-fitting structure varied from four at baseline (with 47% of variance), three at months 12 and 36 (respectively, explaining 41% and 49% of variance), and five at month 24 (59%). Here, only the pairing constituted by agitation and irritability found in AD and in the total samples was confirmed, while the other symptoms tended to load on differing components/factors: there was an overlap of psychotic and affective components (i.e., depression with delusions and/or apathy, hallucinations with anxiety), and overlap of elation and/or disinhibition and aberrant motor behaviour to the hyperactivity elements.

2.4.6. Results of longitudinal analyses

The same interpretation methods and criteria described above for the main analyses (in which sample size was optimised for each time point) were applied to this set of analyses (where the same set of participants were present for all time points). In Appendix A is reported the best-fitting models of the principal component and factor analyses for the AD group and MCI group.

Similar results were found when analysing these longitudinal samples as were found for the main analyses. Specifically, the components/factors were again seen not to be entirely consistent over time. However, some pairings did emerge, which corresponded with those identified in the main analyses. The main difference found was in the number of component/factors identified (see below), which may be due to the differences in

sample sizes between the two analyses (with the longitudinal one having smaller samples overall).

Only baseline and month 12 could be analysed for the AD sample, which consisted of 147 participants (Appendix A). A four component/factor structure best fitted the data, and the most consistent pairings were agitation with irritability, depression with anxiety, elation with disinhibition, and sleep with appetite, while delusions and hallucinations only paired together at baseline, and overall, the composition of the components/factors and the clustering of other symptoms varied substantially.

Lastly, concerning the MCI at baseline sample (with subsequent time points including participants who remained at MCI and those who developed AD), were analysed up to month 36 (Appendix A). In this case, the first three time points were better described by a four component/factor structure, while at month 36, five components/factors better fitted the data. Similarly to the main analyses, the components/factors were not consistent over time. Agitation with irritability remained the only pairing identified in the AD group which was consistently found in this MCI group as well. Sleep with appetite, and elation with disinhibition were identified at most time points, and new pairings emerged which were not identified in the AD group, of hallucinations with anxiety, and depression with delusions, apathy, and/or appetite.

2.5. Discussion

To the author's knowledge, this is the first study which investigates the factors of neuropsychiatric symptoms over several time points and within distinct samples of Alzheimer's disease dementia and Mild Cognitive Impairment. In line with previous research (Bettney et al., 2012; Connors, Seeher, et al., 2018), the results indicate that a single unique structure cannot be identified, as the factors derived were not consistently stable, suggesting that there is variability over time (introduced, for example, through sample heterogeneity and the disease stage of the participants). It should be noted, however, that a selection of symptoms did load together for most time point measurements: some consistently across both the AD dementia and MCI groups, while others only within one of the two groups, indicating a tendency of those symptoms to co-occur.

Comparable conclusions can be drawn from the longitudinal analysis, when analysing the participants who had measurements available at all the time points selected (results tables can be found in Appendix A). In those analyses, by reducing the heterogeneity of the samples, through exclusion of participants who dropped out of the study at subsequent time points (for reasons unknown and not recorded in the dataset), similar to the main analyses, a single unique structure could again not be identified. Across the analyses, comparable pairings of symptoms tended to be seen over time, some consistently across AD dementia and MCI groups, and others specifically for one of the two groups, while other symptoms showed substantial variation over time (in all participant groups).

Starting by considering the number of factors/components that represented the best-fitting model, compared with previous studies, this was only partially consistent: while a four-factor structure has been most commonly proposed (e.g., Aalten, Verhey, et al., 2007; Hollingworth et al., 2006), in the latest time points of the AD and total sample subgroups, the data of this study was better interpretable (i.e., presenting less cross-loading symptoms over multiple factors, and/or factors explained by only one variable) with fewer factors, such as three or two. This might relate to the more limited sample-size available for those analyses (see limitations section below), compared to the earlier time points, however, this tendency of identifying fewer factors over time was not reflected within the MCI subgroup analyses, for which the sample sizes also decreased. Therefore, it might more likely indicate a tendency of neuropsychiatric symptoms to be more intercorrelated and less clear over time. This pattern might rather relate to the progression of the neurofibrillary tangle neuropathology explained in chapter 1 (Ehrenberg et al., 2018; Nelson et al., 2023; Tu et al., 2017). While at earlier stages of disease the symptoms manifested are more heterogeneous, which might explain why clearer syndromes were identifiable at the initial measurements, studies that have investigated the correlation between neuropsychiatric symptoms and advanced neuropathological changes (e.g., Nelson et al., 2023) have identified the presence of several overlapping symptomatologic dimensions (more than eight symptoms experienced by each individual). This study's results seem to be consistent with this notion: as the pathology advances, neuropsychiatric syndromes that appear to be distinguishable at earlier stages of the disease tend to overlap in their presentation.

2.5.1. Symptoms relating to hyperactivity

Agitation and irritability, two of the most prevalent symptoms in samples of both MCI and AD participants, were one of the most consistently paired symptoms over time and when considering the groups of MCI and AD participants together and separately. These symptoms were also found to load on the first component/factor (therefore were responsible for the majority of the variance explained) quite consistently across measurements. This was also the cluster which was most consistently confirmed by the longitudinal analyses of both AD dementia and MCI samples, and it was identified in both groups at all time points. Identification of this factor is also in line with the majority of the literature (Hiu et al., 2022), which has proposed a 'hyperactivity' component, that is also evident during the MCI stage (De Vito, Calamia, Weitzner, Bernstein, et al., 2018). The stability of this clustering over time has been previously proposed by two studies on AD samples that performed factor analyses over a two-years and three-years period of time (respectively) (Bettney et al., 2012; Connors, Seeher, et al., 2018), however in Connor, Seeher, et al., (2018), these were typically found together, in clusters comprising also of other symtpoms. The clustering of these symptoms has in fact been typically reported as independent (Hollingworth et al., 2006; Serra et al., 2020), or inclusive of other symptoms such as aberrant motor behaviour (Aalten, Verhey, et al., 2007). In this study, these were found to cluster together quite often with depression and anxiety, particularly in AD (Garre-Olmo et al., 2010; Mirakhur et al., 2004), and with aberrant motor behaviour, disinhibition, and elation more frequently in MCI.

2.5.2. Symptoms relating to impulse control and hypomania

Disinhibition and elation were frequently identified together as a unique cluster in the AD group, which could be termed a 'impulse control' or 'hypomanic' component, previously identified in other studies (e.g., Mirakhur et al., 2004). In MCI, however, they did not load together, but instead, at various time points, in particular for disinhibition, there was overlap with the hyperactivity symptoms mentioned above, similar to what was previously found by Kang et al. (2010) (agitation, irritability and disinhibition) and Truzzi et al. (2013) (irritability, disinhibition and elation/euphoria). Both symptoms were also found to load with aberrant motor behaviour. Similar results were found in the longitudinal analysis of the AD group, while in the MCI group, these symptoms still

tended to load together at most time points, albeit frequently in the same factor as aberrant motor behaviour.

2.5.3. Symptoms relating to affect and mood

The 'affective' symptoms of anxiety and depression were found to load together mostly within the AD group. Other than presenting with high comorbidity in psychiatric conditions (Groen et al., 2020) underlined by key neurobiological mechanisms, for example, linked to synaptic disruption (Wu et al., 2017), an association between these two symptoms is supported by previous factor analyses in AD (Aalten, Verhey, et al., 2007; Bettney et al., 2012; Colombo et al., 2007), and was generally confirmed in this study. In terms of their associations with other symptoms, over several time points they clustered with hyperactivity-related symptoms, and on some occasions with one or both psychotic symptoms (delusions and hallucinations). In MCI, however, they only clustered together at baseline; interestingly, both symptoms were found to cluster with psychotic symptoms in the MCI group, but with different patterns: anxiety with hallucinations, and both affective symptoms, but mostly depression, with delusions. Similar patterns were also observed in the longitudinal analyses: while in AD, they clustered together at both time points, in MCI they were associated with psychotic symptoms in the same manner as in the main set of analyses. Associations between affective symptoms and psychotic symptoms in psychiatric conditions are well established in the literature (Hartley et al., 2013); furthermore, previous studies on AD populations have proposed an association between depressive symptoms and psychotic symptoms, moderated by genetic factors, (e.g., Wilkosz et al., 2007; Wilkosz et al., 2006) and between depression and delusions specifically (e.g., Bassiony et al., 2002; Mizrahi et al., 2006). However, previous factor analyses on neuropsychiatric symptoms within AD dementia and MCI have not typically reported this distinct clustering, and particularly the association between hallucinations and anxiety within the context of MCI has not been investigated in depth so far. Lastly, depression was also found to load with apathy, mostly in MCI and in the total sample; this pairing was previously proposed by a study which investigated a sample inclusive of MCI and AD dementia participants (Apostolova et al., 2014), as well as studies which focused on AD participants only (e.g., Cheng et al., 2012; Hollingworth et al., 2006). Further clarity on the relationship between depression and apathy is currently a matter of investigation

(Lanctôt et al., 2017): the two symptoms share commonalities in their clinical presentation, to the point of having partially overlapping diagnostic criteria (Tascone & Bottino, 2013), which has made them hard to distinguish within the context of AD. However, recent studies (Lanctôt et al., 2023; Mortby et al., 2022) suggest that particularly in AD, they ought to be considered as two distinct syndromes, based on aspects such as: their neurobiological origins, behavioural features, and associations with other neuropsychiatric symptoms (for example, depression but not apathy tends to associate with anxiety, while apathy but not depression with aberrant motor behaviour). A further argument for the distinction between the two symptoms has also been made when considering the association of apathy and depression with anosognosia (which describes when someone is unaware of their disorder or when they underestimate its affects) within the context of AD: while apathy appears to increase with anosognosia, depression correlates with lower anosognosia (therefore higher awareness) (Mograbi & Morris, 2014).

2.5.4. Psychotic symptoms

A ‘psychotic’ cluster (delusions and hallucinations) within AD has been previously suggested, based on genetic findings (Hollingworth et al., 2012), as seen in chapter 1, and previous factor analyses, which quite consistently identified them typically as a stand-alone factor/component (Apostolova et al., 2014; Hollingworth et al., 2006; Nagata et al., 2016), at times inclusive of other symptoms, for example, sleep (Aalten, Verhey, et al., 2007) or disinhibition (Serra et al., 2020). This was confirmed in this study’s analyses to a degree: while within the AD group and the total sample group, delusions and hallucinations did frequently cluster together, there was some fluctuation in the stability of their co-occurrence over time, which seems to suggest a degree of difference in terms of underlying mechanisms between the two symptoms, particularly with the progression of AD pathology, as proposed, for example, by neuroanatomical studies (Fischer, 2020). Psychotic symptoms were also found to frequently cluster together with symptoms relating to affect, hyperactivity, hypomania, sleep, and aberrant motor behaviour, and particularly at the latest time points, where presumably AD pathology was greater, they tended to form part of larger clusters inclusive of different symptomatologic dimensions (for example, factors/clusters inclusive of hyperactive, affective, and psychotic elements). Lastly, as mentioned above, co-occurrence with

depression and anxiety were particularly relevant within MCI, and the nature of these associations at this stage of the disease would be interesting to explore further.

2.5.5. Apathy

While it did co-occur with several other symptoms, a clear and stable relationship to other symptoms could not be identified in the analysis of this study for the symptom of apathy. This seems to be in line with previous factor analyses, which tend to find apathy to either load over multiple factors, or to constitute a stand-alone factor (Hiu et al., 2022). Despite this being the case in this study at some time points, some correspondence could be identified between apathy and appetite, which has been previously suggested (Aalten, Verhey, et al., 2007; Bettney et al., 2012; Nagata et al., 2016; Selbæk & Engedal, 2012) and might relate to the lack of motivation to eat (Mortby et al., 2022). Apathy was also found to be associated with depression, as mentioned above, particularly in MCI, and with aberrant motor behaviour. Considering that apathy is one of the most prevalent and clinically relevant symptoms, further investigations to clarify its origins and co-occurrence with other neuropsychiatric symptoms would be useful.

2.5.6. Aberrant motor behaviour

Similarly to apathy, aberrant motor behaviour did not co-occur with other symptoms frequently enough to be identified within a single component/factor. Consistent with the literature, however, the most frequent associations were either with apathy (Connors, Seeher, et al., 2018; Mirakhur et al., 2004), or with symptoms relating to hyperactivity and disinhibition (Bettney et al., 2012; Cheng et al., 2012; Colombo et al., 2007; Kang et al., 2010).

2.5.7. Sleep and appetite disorders

A co-occurrence of ‘neurovegetative’ symptoms (sleep and appetite disorders) was identified within the MCI samples. As there are not many factor analyses available that focus on MCI only, and this cluster has not been previously suggested (De Vito, Calamia, Weitzner, Bernstein, et al., 2018), it might be interesting to investigate further, considering their established interrelated associations, explained by hormonal models underpinning the mechanisms of these two functions (Liu et al., 2022). Within AD and the total samples, on the other hand, these two symptoms were found to fluctuate on

different factors, which is not uncommon across the literature (e.g., van der Linde et al., 2014). As mentioned, appetite disorders were most frequently linked with apathy. Sleep instead co-occurred with psychosis at some time points, within AD and the total sample. Slightly different results were found in the longitudinal analyses: while in MCI they were still found to load together, in this case they were also found in the same cluster within the AD group, while co-occurring with apathy. While studies on psychiatric conditions, such as schizophrenia, as well as non-clinical populations (Reeve et al., 2015) have suggested an association between different aspects of sleep and delusions and hallucinations, only some previous factor analyses on AD samples found this association of sleep with psychotic symptoms (Aalten, Verhey, et al., 2007; Wadsworth et al., 2012); one longitudinal investigation on AD samples (Bettney et al., 2012) found them to fluctuate over time, as was typically seen in this study, suggesting that further exploration of this association might be interesting. Lastly, it is interesting to note that sleep disorder was the only symptoms that presented with a higher frequency in MCI compared to AD; considering the impact that sleep may have during the earliest stages of the disease, more research is needed to understand the role this plays in the progression of AD pathology (Benca et al., 2022; Ehrenberg et al., 2018).

2.5.8. Limitations

Some limitations should be noted: first, in terms of sample sizes, although all but one of the analyses complied with the minimum sample-size for factor analyses according to frequently applied criteria (Costello & Osborne, 2005; Stevens, 2002), and that one did, however, fulfil the other requirements considered for the adequacy of sample size (Bartlett et al., 1954; Kaiser, 1974), it would be useful to repeat the analyses on larger datasets, with a ratio of at least 20:1 observations per variable, in order to minimise error (Costello & Osborne, 2005). Concerning the MCI samples, although those who developed other syndromes were excluded, both individuals who had MCI at earlier time points and then progressed to AD dementia and those who remained with an MCI classification at later time points were instead included, which given the uncertainty of disease aetiology, might be a confounding factor in terms of symptom co-occurrence and clustering. Therefore, the heterogeneity of the MCI samples should be considered when interpreting the findings of this sub-group, particularly at the latest timepoints. Due to the limitations of sample size and characteristics, further stratification to

account for aspects such as gender, age, education, ethnicity, or genetic profile, was not performed, which would be an interesting future direction.

2.6. Conclusions and implications for the study of psychotic symptoms

In conclusion, although some degree of consistency existed for certain symptom clusters, a single factor structure was not identified across the time points and that fitted both people with AD dementia and MCI, neither in the main analyses, nor in the longitudinal supplementary analysis. Within AD, it was possible to identify clearer syndromes at earlier stages, while at the latest time points, the symptoms tended to overlap in more complex clinical pictures (for example, constituted of hyperactivity, affect and psychotic symptoms). Considered the paucity of investigations in MCI, it would be useful to perform further investigations to explore, for example, the clusters found in this study, which were not previously suggested, such as hallucinations and anxiety, or sleep and appetite disorders.

Considering the application of this study to the investigation of psychotic symptoms, while these were frequently found to cluster together in the AD and mixed groups, there was some fluctuation in the stability of their co-occurrence over time, and they were not found to cluster together in the MCI group. This highlights the importance of considering aspects such as disease stage and heterogeneity of the sample during study design (and recruitment) and/or during the statistical analyses. Importantly, they were also found to frequently cluster together with different symptoms, such as depression, anxiety, agitation, irritability, and sleep disorder, and at later stages of disease they formed part of larger clusters: this seems to indicate that where presumably AD pathology is greater, the neuropsychiatric associations of psychosis tend to be more complex.

Chapter 3 - Neuroanatomical correlates and predictors of psychotic symptoms in Alzheimer's disease: a systematic review and meta-analysis

This is adapted from the paper published in Neuropsychologia. Abbreviations and tables are adapted to be consistent with the thesis; some elements of the introduction were omitted to avoid repetition with the first chapter of the thesis.

Reference: Scarfo, S., Marsella, A. M. A., Grigoriadou, L., Moshfeghi, Y., & McGeown, W. J. (2024). Neuroanatomical correlates and predictors of psychotic symptoms in Alzheimer's disease: A systematic review and meta-analysis. Neuropsychologia, 204, 109006. https://doi.org/10.1016/j.neuropsychologia.2024.109006

3.1. Overview

In chapter 1, in the section that introduced all neuropsychiatric symptoms, a number of key brain regions was identified in association with delusions and hallucinations, based on the results of recent reviews. However, as mentioned in chapter 1, the scope of those was considered limited with respect to psychotic symptoms, as having a wider focus on all neuropsychiatric symptomology, these could not present in sufficient depth the specific associations of all psychotic symptoms and analyse potential discrepancies among the available neuroimaging techniques. A rationale was therefore formed around the need to further investigate the neuroanatomical correlates of the different manifestations of psychotic phenomena within a contemporary and comprehensive systematic review, which accounts for the different neuroimaging and methodological approaches. Addressing objective 2 of this thesis, this systematic review aims to comprehensively capture, analyse, and evaluate the body of evidence that has investigated associations between brain regions/networks and psychotic symptoms in AD. The protocol, created according to the PRISMA guidelines (Page, McKenzie, et al., 2021; Page, Moher, et al., 2021), was pre-registered on OSF (https://osf.io/tg8xp/). Searches were performed using PubMed, Web of Science and PsycInfo and eighty-two studies were included. Based on data availability, a partial coordinate-based meta-analysis (CBMA) was performed on the findings of fourteen studies on delusions. The findings of the systematic review and meta-analysis are presented and discussed in this chapter: the available evidence highlights that key brain regions, predominantly in the right frontal lobe, the anterior cingulate cortex, and temporo-occipital areas, appear to

underpin the different manifestations of psychotic symptoms in AD dementia and MCI. An interpretation of the findings is then provided: the fronto-temporal areas identified in relation to delusions may underpin a failure to assimilate correct information and consider alternative possibilities (which might generate and maintain the delusional belief), and dysfunction within the salience network (anterior cingulate cortex and insula) may suggest a contribution for how internal and external stimuli are identified; the fronto-occipital areas linked to hallucinations may indicate diminished sensory processing and non-optimal predictive processing, that together contribute to misinterpretation of stimuli and misperceptions. Lastly, the chapter ends by discussing the implications of this review's findings, with proposed suggestions for future research.

3.2. Introduction

Psychotic symptoms, i.e. delusions and hallucinations, are highly prevalent and persistive in Alzheimer's disease (AD), at different stages of the pathology continuum (Vilalta-Franch et al., 2013; Zhao et al., 2016). As discussed in chapter 1, due to their detrimental impact, they represent a worthy treatment target (Agüera-Ortiz et al., 2022), and an increasing number of studies has been published in the last three decades to advance hypotheses on their underlying mechanisms. Notable progress has been made in identifying brain areas and networks associated with the presence of delusions and hallucinations in AD dementia and MCI through the application of a range of different neuroimaging techniques. However, clarity is still needed, as a high number of regions has been identified across the studies, producing consistent variability, likely due to methodological differences which are identified and discussed in the following sections. It is the author's belief that a comprehensive and timely review of the studies' findings will contribute to advancing their interpretation and relevance.

3.2.1. The need for a systematic review and meta-analysis

Given the large number of studies that have investigated the brain regions and networks associated with the manifestation of psychotic symptoms in AD, a systematic review and meta-analysis would be highly beneficial and timely. To the author's knowledge, this is the first review to systematically identify and evaluate all of the evidence provided by studies on the associations between brain regions and networks, as assessed by the different neuroimaging modalities, introduced below, while breaking down the literature

into the individual symptoms (delusions and hallucinations) and also considering the findings when treated as part of a psychotic cluster and considering the thematic components of misidentification and paranoia, as introduced in chapter 1.

While several systematic reviews on neuroimaging and neuropsychiatric symptoms exist, they have tackled this issue from different perspectives: some of these, which focus on neuroimaging, typically consider all neuropsychiatric symptoms (Alvez, 2017; Boublay et al., 2016; Chen et al., 2021), consequently providing a narrower breadth of evidence and analysis specific to the psychotic phenomenology. Others have provided an overview of key findings in this particular area (Fischer & Sweet, 2016; Gottesman & Stern, 2019; Ismail et al., 2022; Murray et al., 2014), albeit without adopting a systematic approach to capture and then analyse the entire body of evidence, nor providing meta-analyses on the data derived from the studies as this review aim to do. With delusions being the most studied among psychotic manifestations, likely due to their higher prevalence in AD compared to hallucinations as highlighted in chapters 1 and 2, two informative reviews (Ismail et al., 2012; Reeves et al., 2012) focused on this symptom, but they are now over ten years old, did not cover the literature on hallucinations, or consider the symptoms as a cluster. Furthermore, only one review (Chen et al., 2021), which was focused on a large range of neuropsychiatric symptoms, included a risk of a bias assessment tool to evaluate the quality of the studies included and provide further rigour in the interpretation of the findings of the selected studies.

Given these limitations of previous systematic reviews on the brain regions/networks linked to psychosis and the growing number of studies on this topic, which has seen an exponential surge over approximately the last ten years, an up-to-date and more comprehensive systematic review is much needed.

3.2.2. Neuroimaging techniques in the investigation of psychotic symptoms

In this section, the imaging techniques employed to investigate the neuroanatomical associations of psychotic symptoms in AD are introduced. Magnetic resonance imaging (MRI) has been extensively used in recent years, as it allows the study of grey matter atrophy in people with psychotic symptoms. Typically, voxel-based morphometry (VBM) (Ashburner & Friston, 2009) or surface-based morphometry (SBM) methods (*FreeSurfer*) are used. These techniques enable whole brain analyses (voxel or vertex-wise) to be

carried out or instead allow focus to be placed upon specific brain regions using a Region of Interest (ROI) approach. The MRI has also been used to study the role of vascular lesions, or white matter hyperintensities (WMH), in association with the clinical manifestations of AD (Hirono et al., 2000).

In addition to the results derived from a structural investigation of the brain, functional imaging techniques have been used to study neuropsychiatric symptoms. These techniques allow individual brain regions to be assessed, in addition to the mapping of neural networks. They can be applied during rest (e.g., to reveal intrinsic connectivity networks) or while participants are engaged in tasks requiring higher mental functions. Among these, those most typically used are single photon emission tomography (SPECT) and [(18F)] fluorodeoxyglucose positron emission tomography (FDG-PET), which provide measures of blood flow (perfusion) and glucose metabolism, respectively, and in more recent years, functional magnetic resonance imaging (fMRI), which relies on hemodynamic changes related to underlying cellular activity (Dickerson, 2011; Killiany, 2011; Pihlajamäki & Sperling, 2011).

3.2.3. Potential sources of variability in neuroimaging studies of psychotic symptoms

As mentioned above, several methodological choices are likely to contribute to variability in the findings across studies that attempt to link brain regions to psychotic symptoms. The current review has been designed to record key methodological details of the studies, so that these may be filtered and clustered in order to identify potential sources of variation.

Heterogeneity across neuroimaging techniques and associated analysis methods may be two sources of such variation. For instance, in relation to the analytic approach, in both structural and functional modalities, adopting a region of interest (ROI) approach could yield different results compared to when analysing the whole brain through voxel-based (or vertex-based) techniques (Giuliani et al., 2005). For this reason, the neuroimaging modality and analytic approaches are recorded.

Other factors intrinsic to the studies' designs might present sources of variation across findings. Considering the difference in prevalence rates of psychotic symptoms along the AD continuum (Weamer et al., 2016), one such aspect is the disease stage. This

refers, for example, to whether the associations were investigated in a prodromal or more clinically advanced stage of the disease.

The reliability of results might be influenced by the study sample size, and larger sample sizes are desirable. Initiatives such as the Cache County Study (Steinberg et al., 2008) or the Alzheimer's Disease Neuroimaging Initiative (ADNI) (*ADNI | Alzheimer's Disease Neuroimaging Initiative*, 2026), which collect data from large numbers of participants with AD and cognitively healthy elderly people, allow a variety of analyses to be performed on an extended sample. An expectation might be that they will be more reliable. Still, multi-site studies can come at the cost of having different brands or models of scanners, in addition to software versions, protocols and technical staff across sites (which can introduce variance, for example, in the homogeneity of the scans, and which may, therefore influence the results). The results derived from these larger multi-site studies might, therefore, differ from the results obtained from smaller scale projects, for example, that use a single scanner. The composition of the sample(s) is also likely to play a role (i.e. whether a matched control sample was included in the analysis, and if so, how exactly they were matched).

Furthermore, the presence of psychotic symptoms in AD is commonly assessed using standardised tools, mainly the caregiver-interview Neuropsychiatric Inventory (NPI, or NPI-Q in its shorter, questionnaire, form) (Cummings et al., 1994). However, different means of assessing might be used, as mentioned in chapter 1. The ability of a study to capture the psychotic symptomology is likely to be impacted by the sensitivity and specificity of the tool used; therefore, capturing the instrument used should be beneficial for a comprehensive appraisal of results.

The assessment of psychotic symptoms is also further impacted by an understanding of their phenomenology: as mentioned above, most studies have explored these symptoms focusing either on delusions and hallucinations as individual symptoms or within a psychotic cluster, which was at times also inclusive of other neuropsychiatric symptoms, that were found by some studies to load in the same cluster as delusions and hallucinations, for example: sleep disorders (Aalten, Verhey, et al., 2007; Wadsworth et al., 2012) or agitation (Banno et al., 2014).

Others have investigated different aspects of the symptomology; for example, some exploring psychosis in terms of misidentification (normally inclusive of hallucinations, and delusions of misidentification, Capgras syndrome and phantom boarder) versus paranoia (normally inclusive of delusions of persecution, theft, abandonment and jealousy) as two distinctive subtypes as outlined in chapter 1 (Cook et al., 2003) and investigating their relation to different brain areas (Bruen et al., 2008; D'Antonio et al., 2019). Similarly, the study of delusional subtypes has provided some evidence (Nakano et al., 2005; Nomura et al., 2012; Schroeter et al., 2020) to support that the different content of delusions might relate to distinct underlying processes, and consequently, different brain mechanisms. Lastly, while hallucinations in AD tend to be mostly visual, differences have been reported in terms of brain areas related to the sensorial nature of the hallucination (El Haj et al., 2017).

Given these different approaches to the study of psychotic symptoms, within this review, plan is to provide a highly comprehensive overview by capturing all the neuroimaging literature that either a) groups symptoms into a cluster, b) that separates them into separate symptoms (e.g., hallucinations vs. delusions), or c) which divides symptoms into separate subtypes (e.g., misidentification vs paranoia).

3.2.4. Aims of this systematic review and meta-analysis

The systematic review illustrated in this chapter aims to identify the large number and diverse range of neuroimaging studies that investigate the brain regions and networks that are linked with psychotic symptoms in AD, to record and provide a synthesis of the results, evaluate the findings for a psychotic cluster, and for hallucinations and delusions separately, investigate sources of variation across the findings, and appraise study quality using a validated tool (Joanna Briggs Institute, 2014). Furthermore, depending on the number of included studies, and the homogeneity of methods applied, the potential for meta-analyses will be explored.

3.3. Methods

The protocol for this systematic review has been pre-registered on the Open Science Foundation (OSF) (https://osf.io/tg8xp/).

3.3.1. Search strategy and selection of records

This review was based on the PRISMA protocol (Page, McKenzie, et al., 2021; Page, Moher, et al., 2021), and each step was recorded in a PRISMA flowchart (Figure 3.1). A review of the literature was performed between the 09th and the 30th of December 2021, on the databases PubMed, Web of Science and PsycInfo, using the following terms:

"Psychosis" OR "Psychotic" OR "Neuropsychiatric" OR "NPS" OR "Behavioural" OR "Behavioral" OR "BPSD" OR "Delusion*" OR "Hallucination*" OR "Misidentification" OR "Persecut*" OR "Capgras"

AND

"Alzheimer's" OR "AD" OR "MCI" OR "Mild cognitive impairment" or "Dement*"

AND

"Neuroanat*" OR "Neuroimaging" OR "MRI" OR "Magnetic Resonance Imaging" OR "fMRI" OR "Functional Magnetic Resonance Imaging" OR "Positron Emission Tomography" OR "PET" OR "Single Photon Emission Computed Tomography" OR "SPECT" OR "Voxel-based Morphometry" OR "VBM" OR "Cortical Thickness".

All records retrieved were imported from the databases into an ad-hoc developed Endnote library; duplicates were removed both automatically (through Endnote import procedures), and manually by one of the researchers. This led to the selection of three thousand nine hundred and ninety records, which were screened for titles and abstracts by two independent reviewers (Figure 3.1), according to the following eligibility criteria: 1) eligible studies were either cross-sectional studies (which investigated the association between affected brain regions/network and psychotic symptoms), or longitudinal studies (which investigated the brain regions/networks that when affected, predict future manifestation of psychotic symptoms); 2) they contained samples of people with Alzheimer's disease and/or Mild Cognitive Impairment, and had a focus on delusions or hallucinations (either independently, or as part of broader analyses on psychotic symptoms or neuropsychiatric symptoms); 3) eligibility was limited to publications in English and peer-reviewed publications, but with no restrictions on publication date.

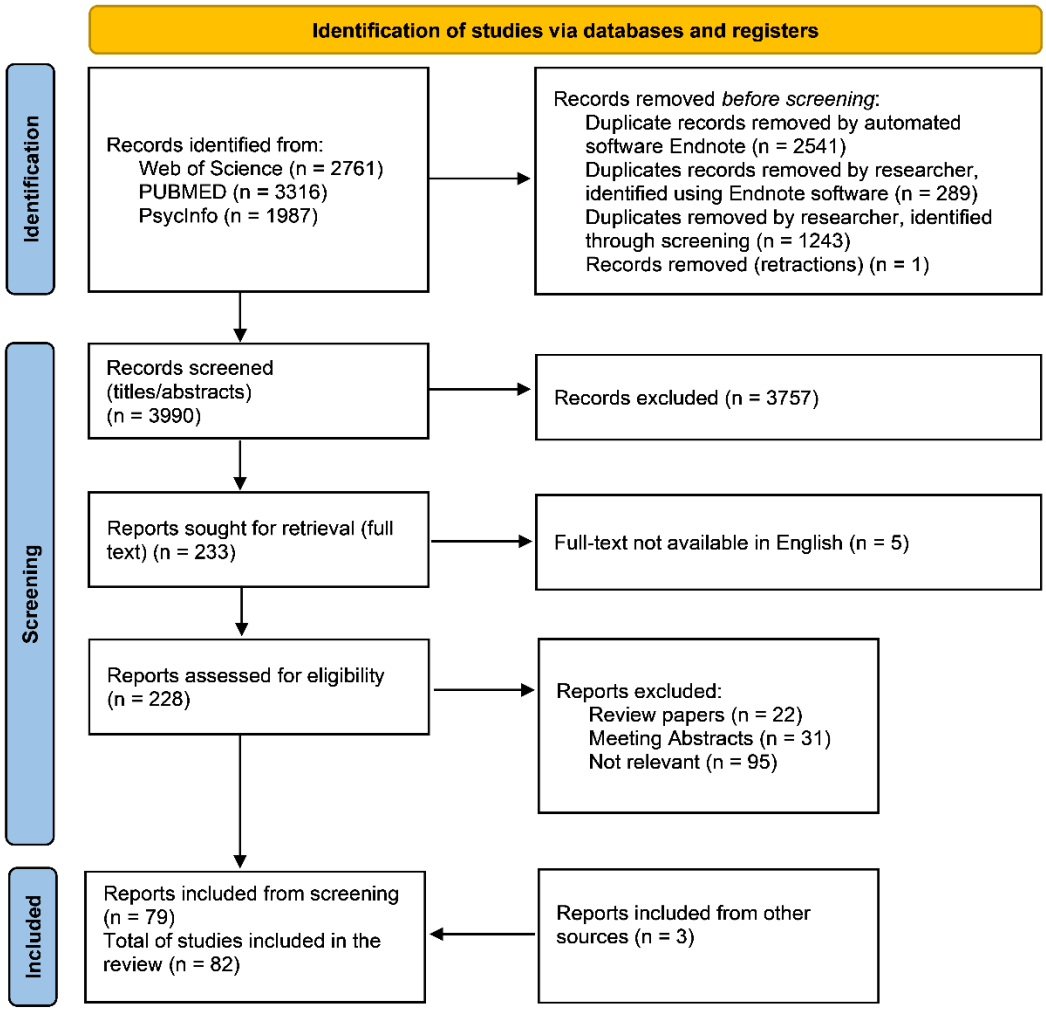
Two hundred and thirty-three records were deemed relevant from the screening: five of these were not available in English and were therefore excluded, while the remainder two hundred and twenty-eight were retrieved in full text to be assessed for eligibility by two independent reviewers; these led to the inclusion of seventy-nine records. Three additional studies were selected from the screening of reference lists of relevant studies and reviews, limited to studies published before the 30th of December 2021 (Figure 3.1).

For completeness in relation to literature capture, case studies were included in the systematic review, and their findings are presented in the tables and results section. However, when performing a holistic appraisal of regions/networks most commonly identified across the literature, only studies containing analyses with multiple participants were considered.

Agreement on the inclusion of records between the reviewers was tested using Cohen's Kappa inter-rater reliability assessment (Cohen, 1660), after both independent selections of titles and abstracts and then full texts; this was performed on IBM SPSS Statistics (Version 28) (IBM Corp., 2021), with moderate results (titles/abstracts: κ=0.562 [95% CI, 0.614 to 0.51], p<.001; full texts: κ=0.663 [95% CI, 0.759 to 0.567], p<.001). Where discrepancies arose, these were resolved through discussion of the individual studies, and full agreement was subsequently reached at both stages.

Figure 3.1

Prisma flowchart



3.3.2. Quality assessment of included studies

The studies included in the review were assessed for risk of bias, using a validated tool deemed fit for this type of data (Ma et al., 2020): the Joanna Briggs Institute Critical Appraisal Tool Checklist for Analytical Cross-Sectional Studies (Joanna Briggs Institute, 2014) (see Appendix B for reported Checklist and instructions for application).

The items of the tool were: 1. Were the criteria for inclusion in the sample clearly defined? 2. Were the study subjects and the setting described in detail? 3. Was the exposure measured in a valid and reliable way? 4. Were objective, standard criteria used for measurement of the condition? 5. Were confounding factors identified? 6. Were strategies to deal with confounding factors stated? 7. Were the outcomes measured in a valid and reliable way? 8. Was appropriate statistical analysis used?

These were applied to each study by two independent reviewers, with the purpose of assessing their methodological quality, and determining the extent to which the possibility of bias was addressed in their designs and analyses. Any case of discrepancy between the two reviewers was resolved through discussion, and agreement on the score of all items was reached.

3.3.3. Data extraction

An ad hoc protocol for data extraction was designed in order to extract the data which was considered most informative and potentially useful for synthesis. The protocol allowed details of the sample and design of the studies to be captured, along with a clear categorisation of the symptom studied; the characteristics of the neuroimaging technique employed; and clear details on the statistical analysis performed. More specifically, the following headings were included in the protocol, which reflected elements for summarisation, and that may be potentially useful for synthesis, and/or likely to impact the findings and inform their interpretation: Author(s) and Year, Symptom(s), Participants, Design(s), Neuroimaging Techniques and Metrics, Aim(s), Confounding Factors, Brain Area(s) Investigated, Statistical Threshold and Correction, Relevant Findings. For better readability of the tables, the additional columns AD Diagnosis (specifying criteria used), Disease Stage, Symptom Rating Scale or Assessment Method used for Psychotic Symptoms, Type of Scan and Analysis Software are only included in the digital version of this table (which is available in the OSF folder linked to this thesis).

With regard to the symptomology, this was divided into the three main groups of delusions, hallucinations, and psychotic cluster, with the latter referring to the studies that used the approach of selecting a combined sample inclusive of participants presenting with delusions and/or hallucinations, and any additional symptoms

considered within the cluster. The subtype of delusions and hallucinations was also further specified for those studies that reported this information.

3.4. Results

3.4.1. Descriptive features

The data extracted from the eighty-two studies highlighted an upward trend in the year of publication, with 61% studies published in the last decade only (n=50), from 2011 to 2021 and the remaining 39% (n=33, from 1991 to 2010) extending to the previous two decades.

In terms of frequency of neuroimaging technique, the most common was structural MRI (n=47), mainly used to assess grey matter (n=40) and white matter (n=2) atrophy, with either regional or whole brain (voxel-wise or vertex-wise) analyses, white matter changes assessed through the Age-Related White Matter Changes (WMC) Scale (Wahlund et al., 2001) (n=2), and presence of White Matter Hyperintensities (WMH) (n=10); this was followed by SPECT (n=17) and PET (n=15), and less commonly fMRI (n=5) and CT (n=4).

Forty-nine studies investigated delusions and in n=17, analyses were focused on one or more delusional subtypes (e.g., Capgras syndrome, misidentification, persecutory, etc.). Twenty-five studies investigated hallucinations. Concerning the composition of the samples, the presence of other psychotic or neuropsychiatric symptoms was rarely reported, with few exceptions. Specifically, among the studies that investigated delusions, one study, in which the sample with delusions might also have had hallucinations, specified that the control (non-delusional) sample did not present with hallucinations, and two studies reported that other neuropsychiatric symptoms were present in their samples (who had delusions), and these were considered in the analyses; similarly, among the studies that investigated hallucinations, one considered the presence of other neuropsychiatric symptoms, and within the studies on psychotic symptoms, one considered non-psychotic neuropsychiatric symptoms in the analyses. Within the remaining studies, this information was not available. Lastly, a considerable number of studies classified participants according to a psychosis symptom cluster (n=26). In the associated analyses, participants were classified as being in a psychosis group, irrespective of what type of psychotic symptom they had (e.g., there were not separate subgroups for delusions and hallucinations). In three cases, one other

neuropsychiatric symptom was also found to load on a psychosis-themed factor (in two studies this was sleep disorders and in one disinhibition).

In Appendix B, a summary of the studies which reported significant and non-significant findings is provided, reported according to the targeted symptoms and the neuroimaging technique employed (with further specification for MRI in terms of analysis method).

In terms of assessment of the symptoms, the most common standardised tool was the Neuropsychiatric Inventory (NPI) (n=44), followed by its shorter, questionnaire, version, the NPI-Q (Cummings et al., 1994) (n=10). Other assessment tools included the Neurobehavioural Rating Scale (Levin et al., 1987) (n=4), and the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al., 1987) (n=3); on some occasions, no standardised tool was employed, and the symptom classification was based either on the application of DSM (American Psychiatric Association, 1987, 1994) (n=5) or Jeste and Finkel (Jeste, 2000) (n=2) criteria, or on observation of the clinical picture (n=5) and unstandardised interviews (n=2).

The sample size was commonly between 5 and 30 participants with psychotic symptoms, with few exceptions: case studies, as well as some studies with a broader focus on many different NPS, had only 1 or 2 participants with psychotic symptoms, while the highest sample of participant with the symptoms (as a cluster) was 79. The studies were varied in terms of disease stage, with some studies focusing on specific levels of severity (MCI and/or specifically amnestic MCI, or mild, moderate, or severe AD dementia) and others including some or all of those.

Diagnosis of probable AD was almost always made on the basis of NINCDS-ADRDA criteria (n=74) (McKhann et al., 1984), often supported by the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (n=20) and Clinical Dementia Rating Scale (CDR) (Morris, 1993) (n=13) and in more recent studies (n=5) NIA-AA criteria (Jack et al., 2018). MMSE and CDR were also frequently employed to determine the severity of the disease stage.

3.4.2. Holistic appraisal

An overall analysis of all regions and networks that were most commonly found across all neuroimaging techniques and symptomatologic dimensions, highlighted that some key areas appear to underpin the manifestation of psychotic phenomenology in AD: these are mainly regions in the frontal lobe, and in the limbic system; nevertheless, associations were also found with brain regions in the temporal, parietal and occipital lobes, and in subcortical structures. There was a slight predominance of associations to the right hemisphere.

Table 3.1 presents an overview of the most common regions that were identified to have associations with the symptoms of interest, grouped by psychotic symptomology, and structural and functional neuroimaging technique.

Table 3.1

Brain regions and networks identified in association with psychotic symptoms

Symptom group	Structural measures - grey and white matter atrophy, areas of white matter hyperintensities (MRI and CT)	Functional measures – hypo/hyper metabolism, hypo/hyper perfusion, haemodynamic changes (PET, SPECT, fMRI)
Delusions	Frontal Lobe Superior, Middle, Medial and Inferior Frontal Gyri (bilateral) *8* Orbitofrontal Cortex (bilateral) *2* Temporal Lobe Superior Temporal Gyrus (bilateral) *4* Parahippocampal Gyrus (bilateral) *2* Parietal Lobe Precuneus (L) *2* Occipital Lobe Inferior and Middle Occipital Gyri (bilateral) *2* Other Brain Regions Anterior Cingulate Cortex (R) *4* Posterior Cingulate Cortex (R) *3* Insula (bilateral) *3* Basal Ganglia (Putamen) (bilateral) *2* Cerebellum (bilateral) *3*	Frontal Lobe Superior, Middle, Medial and Inferior Frontal Gyri (bilateral) *11* Orbitofrontal Cortex (bilateral) *5* Prefrontal Cortex (R) *3* Temporal Lobe Superior, Middle, Medial and Inferior Temporal Gyri (bilateral) *12* Parietal Lobe Precuneus (bilateral) *3* Occipital Lobe Middle and Medial Occipital Gyri (bilateral) *2* Other Brain Regions Anterior Cingulate Cortex (bilateral) *2* Posterior Cingulate Cortex (bilateral) *3* Insula (bilateral) *2* Basal Ganglia (Putamen) (bilateral) *2*
Hallucinations	Frontal Lobe Superior and middle Frontal Gyri (bilateral) *2* Temporal Lobe Parietal Lobe Occipital Lobe Other Brain Regions Anterior Cingulate Cortex (R) *2*	Frontal Lobe Temporal Lobe Parietal Lobe Occipital Lobe
Psychotic cluster	Frontal Lobe Superior, Middle, Medial and Inferior Frontal Gyri (bilateral) *6* Orbitofrontal Cortex (bilateral) *2* Temporal Lobe Parahippocampal Gyrus (bilateral) *2* Hippocampus (R) *2* Entorhinal Cortex (bilateral) *2* Parietal Lobe Occipital Lobe Lingual Gyrus (bilateral) *3* Other Brain Regions Anterior Cingulate Cortex (bilateral) *2*	Frontal Lobe Orbitofrontal Cortex (bilateral) *2* Temporal Lobe Parietal Lobe

Notes. All reported regions were identified by at least 2 studies with multiple participants (case studies are excluded); *n* indicates the exact number of studies which mentioned this region.

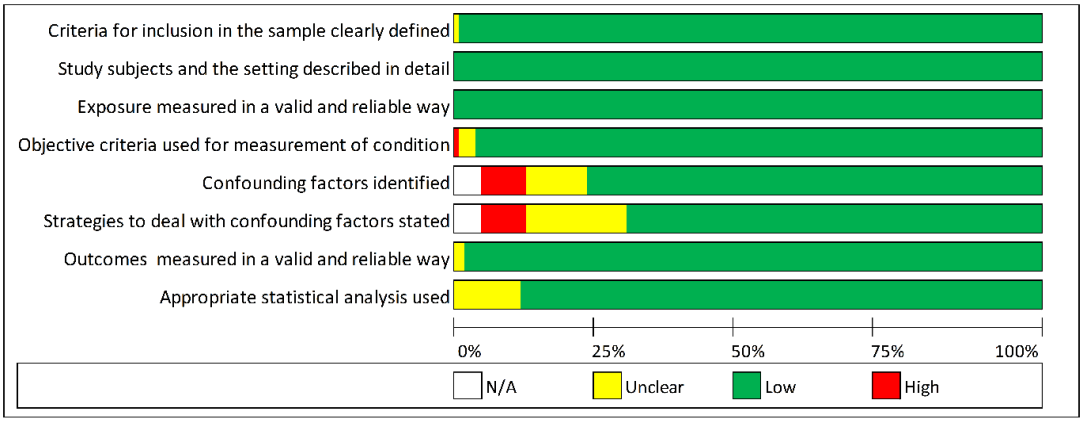
When only the lobe is listed, without a specific brain region provided beneath, it signifies that the lobe was mentioned in the findings from more than two studies, however, either no further specifics were provided on location, or the studies reported different brain regions within the lobe.

3.4.3. Quality appraisal: risk of bias assessment

Figure 3.2 depicts a visual representation of holistic appraisal performed using the risk of bias assessment tool (Joanna Briggs Institute, 2014). This showed that the overall quality of the evidence according to the criteria of this tool was high, as more than two thirds of the studies scored positively across all items.

Figure 3.2

Visual depiction of the results of the JBI risk of bias assessment tool



Notes. Exposure measure here refers to a factor that may be associated with the outcome of interest; in the case of this review, this referred to the neuroanatomical features and whether they were measured in a valid and reliable way with respect to the imaging approach employed. Outcomes were considered the different classifications of psychotic symptoms.

It also allowed reflection on the main aspects of variability revealed by this assessment: whether each study considered potential confounds, and if they adopted strategies to take their impact into account (e.g., by including these as covariates in the analyses). The severity of disease, most commonly measured with the MMSE (n=37), CDR (n=16),

or Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) (Mohs, 1994) (n=4) was one of the most commonly used, normally alongside age (n=47), and at times other aspects such as gender (n=30), years of education (n=24), and duration of illness (n=14).

About two thirds of the studies (n=37) explicitly stated controlling for or considering factors in relation to the imaging technique; in the MRI, the most common was the total intracranial volume (n=26), while a small number of PET and SPECT studies stated use of mean glucose metabolism/blood flow rate (n=6). One potentially important aspect that was only considered in a small number of studies, was the overall neuropsychiatric picture of the sample, particularly for the studies which focused on delusions and hallucinations independently, it is mostly unclear whether the presence of the other symptom was considered. While the majority of the studies considered at least one, and more frequently combinations of those factors (most commonly disease severity, age, gender, and aspects relating to the imaging technique employed, such as total intracranial volume), in about a third of the studies whether these types of factors were included in the analyses, was not specified in the studies.

Another aspect of variability was the level of detail provided when reporting the statistical analysis methodology, in reference to the significance threshold and/or methods applied to account for multiple comparison: while the majority of the studies reported the significance threshold applied, fewer provided details either on the methods applied to correct for multiple comparisons, or stated a reason why such correction was not necessary. A smaller number of studies, however, did not specify either type of information.

In the following sections, the findings of the studies will be synthesised based on the psychotic symptom investigated and within that, on the neuroimaging technique employed. The majority of the studies included participants presenting with AD dementia; for the studies that also included MCI participants, this will be explicitly stated. Most studies focused on the neuroanatomical features associated with the presence of the symptom of interest; on the occasions where the focus differed (e.g., longitudinal studies which considered the development of the symptom, or studies which focused on the intensity or severity of the symptoms), this will be noted.

3.4.4. Delusions

Results are summarised in Table 3.2.

3.4.4.1. Grey matter atrophy: results from MRI – VBM

The most common method to assess grey matter atrophy with MRI, was to investigate associations with delusions using voxel-based morphometry (VBM). This technique was used in nine studies, with four including a longitudinal assessment. The majority reported involvement of frontal and temporal regions, and the limbic system, more commonly with right-side predominance. Among the longitudinal investigations, one study (Boublay et al., 2020) identified an association between the future development of delusions and the right anterior cingulate cortex: this region was also identified by Nakaaki et al. (2013b), as well as the right posterior cingulate, which was also found in Fischer et al. (2016). The two aforementioned studies (Fischer et al., 2016; Nakaaki et al., 2013b) also similarly identified associations with the parahippocampal gyrus, and insula, bilaterally, however Fischer et al. (2016) identified the majority of regions to be in the left hemisphere. Qian et al. (2019a) partially confirmed previous findings, with clusters found in the left precentral and middle frontal gyri (also in Nakaaki et al. (2013b)) when comparing delusional and non-delusional participants; they also interestingly found differences from baseline to follow-up in those who developed delusions compared to those who did not in frontal and temporal lobes, along with single clusters in the precuneus, cerebellum (also in Fischer et al. (2016)), occipital lobe and putamen, and they showed an accelerated decrease of temporal grey matter atrophy in the group with delusions compared to the controls.

Table 3.2

Studies on Delusions

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Anor et al., 2017	delusions**	67 AD, 9.1% delusions; 38 mixed AD/ VaD, 20.8% delusions	cross-sectional	MRI, WMH	differences in incidence of NPS, in relation to frontal WMH volume	age	frontal lobe, in Atlas of the Human Brain	$p<.05$	greater WMH volume in the R frontal lobe, compared to those without delusions
Anor et al., 2021	delusions**	138 AD, 114 MCI-AD, from 7.1 to 20% incidence delusions	cross-sectional and longitudinal (at 1 year)	MRI, WMH	relationship between NPS, and WMH burden in MCI-AD or AD patients; relationship between WMH volume and future development of NPS	use of psychotropic medications; total volumes of MRI scans normalised for head size	load of WMH on whole brain	FDR to correct for multiple comparison	whole brain WHM load (future delusions severity sub-scores)
Berlow et al., 2010	delusions**	37 AD, 12 delusions	cross-sectional	MRI, WMH, VBM	association between NPS in AD and: volumetric reduction of grey matter (of whole brain and hippocampus) and increase in white matter changes (WMH)	age, MMSE; skull size	whole brain and hippocampus	$p<.10$	trend (did not reach significance) with WMH load
Boublay et al., 2020 *	delusions**	53 AD, 7 delusions; 40 healthy controls	longitudinal	MRI, VBM	regional brain volumes of the whole brain and behavioural changes (mild stages of AD)	gender, age; type of MRI	whole brain, in MNI space	$p\leq.001$	smaller brain volume in R anterior cingulate cortex
Bruen et al., 2008	delusions (misidentification) ***	31 mild AD, 16% delusions	cross-sectional	MRI, VBM	decreased grey matter volume in association with NPS in patients with mild AD	age, number, education, MMSE; correction for global differences in brain shape	whole brain	$p<.01$	low GM density values in R inferior frontal gyrus, R inferior parietal lobule, L inferior and medial frontal gyri, and in the claustrum

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Fischer et al., 2016 *	delusions	24 AD delusions	cross-sectional and longitudinal	MRI, VBM	grey matter changes pre and post delusion onset	not specified	not specified, in Talairach and Tournoux Atlas	p<.05 with no masking, corrected by FDR	grey matter decreases in R and L insular, L precuneus, R and L cerebellar culmen, L superior temporal gyrus, R posterior cingulate, R thalamus, L parahippocampal gyrus
Förstl et al., 1991	delusions (Capgras, misidentification)	130 AD, 2 Capgras, 40 misidentification, 88 without delusions	case-study	CT, ROI	relationship between CT measurements in AD patients and the forms of misidentification	cognitive impairment, duration of disease age; differences in skull size, global brain atrophy	third, R and L anterior horn ventricles, R and L anterior and posterior brain (quadrants)	not specified	R frontal atrophy, significantly larger L frontal lobes (L anterior quadrant) and larger R anterior horns
Fukuhara et al., 2001 *	delusions (theft)	18 AD, 9 delusions of theft and 9 without delusions	cross-sectional	SPECT, VB	delusions of theft in relation to regional cerebral blood flow	age, years of education and neuro-psychological tests	whole brain	p<.01 uncorrected (clusters with p<.05 probability)	hypoperfusion in R medial posterior parietal region
García-Alberca et al., 2019	delusions**	46 AD, 9 delusions	cross-sectional	MRI, MTA, WMH	relationship between WMH and MTA observed on MRI and specific NPS in patients with AD	age, gender, education, duration of disease, diabetes mellitus, hypertension, heart disease, MMSE	WMH in frontal, occipital, lateral periventricular, frontal parietal, temporal and occipital deep subcortical, basal ganglia, infratentorial lesions; L and R MTA volumes	p< 0.05	no significant results
Geroldi et al., 2000	delusions (theft and paranoid)	19 AD patients with delusions and 22 without	cross-sectional	CT, WTH	delusions in association with asymmetric involvement of the temporal lobe regions in AD	sociodemographic and clinical features	temporal lobe	not specified	greater R than L temporal horns
Hirono et al., 1998	delusions (persecutory, misidentification, jealousy) ***	65 AD patients, 26 delusions	cross-sectional	FDG-PET, ROI	AD patients with delusions present distinct features in regional cerebral metabolism	mean value of all cortical metabolic rates for glucose	dorsolateral and basal prefrontal, anterior cingulate, superior, medial, middle inferior temporal, medial and lateral occipital, inferior parietal	p<.05 corrected for multiple comparison (Bonferroni)	hypometabolism in the L medial occipital region and hypermetabolism in the inferior temporal gyrus
Hořínek et al., 2006	delusions**	30 AD, 11% delusions	cross-sectional	MRI, ROI	association between the reduction of amygdala volume in AD and psychiatric symptoms	age, gender, and level of education; intracranial and total brain volumes	amygdala and hippocampus	p<.05	no significant results

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Jaramillo-Jimenez et al., 2021	delusions**	55 AD, 34 dementia Lewy Body (DLB), delusions 13.7%, 15.5% and 18.2% (Y3 to 5)	longitudinal (baseline, Years 1,2,3,4,5)	MRI, ROI	association between amygdala volumes and longitudinal development of NPS in AD and DLB	gender, diagnosis, MMSE total score, time in study; intracranial volume MRI acquisition centre	amygdala	$p<.05$ corrected for multiple testing (FDR)	no significant results
Jedidi et al., 2015	delusions (Capgras)	51 AD, 1 delusions, 26 without; 24 healthy controls	case-study	MRI and FDG-PET, VBM	functional cerebral correlates of Capgras delusion	age and gender	not specified, in MNI space	$p<.01$ uncorrected	atrophy in posterior cingulate cortex (PCC) and precuneus cortex, and hypometabolic cluster in L dorsal and posterior medial prefrontal cortex (MPFC) and L upper precuneus/PCC (case study compared to healthy controls); hypometabolism of L dorsal posterior MPFC and upper L precuneus/PCC (case study and AD group)
Kotrla et al., 1995	delusions ***	46 AD, 29 delusions, 16 non-psychotic	cross-sectional	SPECT, ROI	delusions and hallucinations in patients with AD associated with cerebral dysfunction in the frontal and parietal lobes	age, education and MMSE	frontal and parietal lobes, six regions of interest per hemisphere; standard atlas to determine anatomic location of each ROI and midventricular slice	not specified	hypoperfusion of the L lateral frontal lobe in the upper and lower slices (compared to R)
Lee et al., 2006	delusions**	55 AD, 10 with psychosis (% delusions not specified)	cross-sectional	MRI, White Matter Changes (Age-Related WMC scale)	relationship between white matter changes seen on MRI and neuropsychiatric symptoms in probable AD patients	age, education, gender, and duration of illness	L and R frontal areas, L and R parieto-occipital areas, L and R temporal areas, L and R basal ganglia	$p<.05$ uncorrected	misidentification: overall white matter changes, L frontal white matter changes, bilateral frontal and parieto-occipital white matter changes, bilateral frontal, bilateral parieto-occipital, and R basal ganglia, bilateral frontal, L parietooccipital and L basal ganglia
Lee et al., 2009	delusions (also confabulations)	22 AD, 13 delusions; 12 healthy controls	cross-sectional	SPECT, VBM	neurologic backgrounds of delusions in relation to confabulations	individual variations	not specified, in MNI space	$p<.05$, corrected by FDR rate	hypoperfusion of R prefrontal cortex

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Lopez et al., 2001	delusions ***	9 AD, 2 hallucinations, 2 delusions, 5 no psychotic symptoms; 9 elderly controls	cross-sectional	PET, ROI	critical brain region that serves as common denominator for the development of psychotic phenomenon in AD	not specified	orbitofrontal, frontal dorsolateral, anterior cingulate, medial temporal, superior temporal, parietal and occipital cortices, and basal ganglia and thalami	not specified	rel-CBF in R and L thalamus
Matsuoka et al., 2010 *	delusions	35 AD, 14 delusions (of which 12 females) 11 without; 7 healthy controls	cross-sectional	SPECT, not specified	brain regions associated with severity of delusions in AD	other NPI subscale scores and MMSE scores, mean cerebral global blood flow	not specified	p<.01, uncorrected, cluster size>50	hypoperfusion of R anterior insula hypoperfusion (with exacerbation of delusions)
Mentis et al., 1995	delusions (misidentification)	23 AD, 9 delusions, 14 without delusions, and 17 healthy controls	cross-sectional	PET, ROI (absolute rCMRglc values)	rCMRglc of AD patients, with delusional misidentification syndromes	inter-subject glucose metabolism (whole brain CMRglc), in the SPM analysis	not specified	p<.05, post hoc Neuman-Keuls	ROI: hypometabolism in bilateral cingulate and basal ganglia (compared to healthy controls); hypometabolism in lateral orbitofrontal, L posterior medial temporal, L anterior and bilateral posterior cingulate, L caudate nucleus, L lentiform nucleus, L calcarine; SPM: hypometabolism in orbitofrontal and anterior cingulate regions, bilaterally, and hypermetabolism in a superior temporal, inferior parietal, and precuneus cortex, bilaterally
Moon et al., 2014	delusions**	40 AD, 14 delusions	cross-sectional	MRI, ROI	association between the volume ratio of the insular cortex and neuropsychiatric symptoms in patients with AD	age, CDR score, vascular risk factor and other NPS; WMH, tot GM volume divided by other NPS, TIV	insular cortex, subdivided into four subregions by the CIS and bilaterally: the R anterior insular cortex, R posterior insular cortex, L anterior insular cortex and L posterior insular cortex	not specified	no significant results

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Nakaaki et al., 2013 (A)	delusions	25 AD, 15 delusions, 10 without	longitudinal	MRI, VBM, Diffusion Tensor Imaging for WM	existence of baseline abnormalities in WM integrity in AD patients who developed delusions and AD patients who did not develop delusions	age, gender, and MMSE score; eddy currents and head movements	whole brain, in MNI space	$p<.05$, corrected for multiple comparisons (threshold-free cluster enhancement)	one (maximum cluster) of reduced fractional anisotropy (FA) in the L parieto-occipital region; one (large cluster) in the body of the corpus callosum; one (minimum cluster) on the R superior temporal gyrus white matter
Nakaaki et al., 2013 (B) *	delusions (persecutory and misidentification)	53 AD, 18 delusions	longitudinal	MRI, VBM	compared the baseline structural brain abnormalities of patients who developed delusions with those who did not	age, gender, education, duration (in years), and MMSE; total brain volume	whole brain	$p<.05$, corrected for multiple comparisons (FDR)	smaller grey matter volumes on both sides of the parahippocampal gyrus, the R posterior cingulate gyrus, the R orbitofrontal cortex, both sides of the inferior frontal cortex, the R anterior cingulate, the L claustrum, and the L insula
Nakano et al., 2005 *	delusions (persecutory, misidentification, jealousy)	64 AD, 25 delusions, 39 without	cross-sectional	SPECT, VB	association between delusions and cerebral deficits in patients with probable AD in a relatively large number of subjects	gender, age at onset, disease duration, and MMSE score; global differences in cerebral blood flow among scans	whole brain, in Talairach and Tournoux atlas	$p<.01$ uncorrected	bilateral frontal lobe hypoperfusion, (R prefrontal cortex, R middle frontal gyrus, R superior frontal gyrus, R inferior to middle temporal cortices, R parietal cortex); persecutory (stealing) vs misidentification: bilateral anterior cingulate gyrus; misidentification: L lingual gyrus and R middle occipital gyrus
Nakatsuka et al., 2013 *	delusions (paranoid, abandonment, Capgras)	54 AD, 27 delusions and 27 without	cross-sectional	SPECT, CBF	clarify delusional subtypes, with the content of delusional ideas corresponding to category-specific sets of neural substrates	age, gender, and MMSE	whole brain	overall delusions: $p<.05$, corrected FWE; cluster size>50 voxels; individual delusional type: $p<.001$, uncorrected	theft: decreased CBF in the bilateral temporal poles (TPs) with R-side dominancy and in the R inferior temporal gyrus; delusion of "not home": decreased CBF in the R amygdala; abandonment: decreased CBF in the R parahippocampal gyrus and R posterior insula; suspiciousness/paranoia: decreased CBF in the bilateral TPs with R-side dominancy

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Nomura et al., 2012 *	delusions (misidentification, persecution, abandonment/ jealousy, theft)	25 AD delusions	cross-sectional and longitudinal	I-MP SPECT, not specified	classified AD delusions and investigated their neural correlates by using single-photon emission computed tomography data	age, MMSE; mean of the tracer uptake in the white matter	whole brain	$p<.01$, uncorrected (normalization to the white matter)	misidentification/abandonment: hypoperfusion R middle temporal gyrus (temporal pole) and hyperperfusion L medial frontal gyrus, L precentral gyrus; persecution: hypoperfusion R precuneus, L precuneus and hyperperfusion L insula, R extra-nuclear, R thalamus, R frontal sub-gyral; abandonment/ jealousy: hypoperfusion R inferior temporal gyrus, and hyperperfusion L middle frontal gyrus, L insula, L putamen (lentiform nucleus), L posterior cingulate gyrus; theft: hypoperfusion L thalamus, R thalamus, L posterior cingulate gyrus and hyperperfusion L inferior frontal gyrus and L anterior cingulate gyrus
Nowrangi et al., 2021	delusions**	72 AD (% of delusions not specified)	cross-sectional	MRI, ROI	decreased volumes of cingulate cortex, frontal and prefrontal lobe structures (including DLPFC), and amygdala with delusions	age, years of education and gender	DLPFC, anterior and posterior cingulate cortex, orbitofrontal cortex, anterior insula, hippocampus, and parahippocampal gyrus	$p<.05$; multiple comparisons (FWE, Bonferroni and Holm)	smaller volume in L ACC including the rostral regions (in severe and mild groups), R subcallosal region (mild); R dorsomedial prefrontal cortex inverse association (moderate)
Ogawa et al., 2013	delusions**	163 AD, 39 delusions	cross-sectional	MRI, WMH	relationship of cerebral SVD observed on MRI with NPS	age, gender, years of education, disease duration, CDR, cholinesterase inhibitor usage	whole brain	$p<.05$ uncorrected	greater SVD (compared to non-delusional)
Palmqvist et al., 2011	delusions**	259 AD, 15% delusions	cross-sectional	CT or MRI, White Matter Changes (Age-Related WMC scale)	independent association between regional subcortical lesions and NPS	cognitive ability; atrophy	frontal lobe anterior to the central sulcus, the parietooccipital	entry limit was $p=.05$, limit of removal $p=.051$ (collinearity reduced by L and R regions separately)	lesions in the basal ganglia (increased risk of delusions)

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Pontón et al., 1995	delusions (including Capgras)	15 AD, 6 delusions and 9 without	longitudinal (at 1 year)	SPECT, ROI	AD patients with delusions will have lower R hemispheric rCBF; difference in rCBF of temporoparietal areas	not specified	inferior temporal gyrus, superior temporal gyrus, prefrontal area, posterior inferior frontal (Broca's) area, temporoparietal area, Brodmann's area 19, cerebellum	alpha set at 0.05, Bonferroni correction for multiple comparisons	higher perfusion in superior temporal gyrus (bilateral), R inferior temporal gyrus. R area 19; uncorrected R inferior temporal gyrus, superior temporal gyrus, area 19, temporoparietal area, posterior inferior frontal area, the prefrontal region, primary visual cortex region; L inferior temporal gyrus, superior temporal gyrus, posterior inferior frontal, prefrontal region, primary visual cortex region
Qian et al., 2019 (A) *	delusions	59 AD, 23 delusions, 36 AD without	cross-sectional and longitudinal	MRI, VBM	grey matter differences associated with delusions in AD, testing the effect of group (delusions against control), time, and interaction between time and group	MMSE, CDR, age, gender, education, and handedness	whole brain	p<.005, voxel-wise followed by cluster size thresholding, minimum cluster size at an adjusted p=.05, multiple comparisons	L precentral and middle frontal gyri, and R supplementary motor area (group); bilateral superior frontal, R inferior orbitofrontal, R prefrontal, bilateral middle temporal, R superior temporal and L inferior temporal, L precuneus, R inferior occipital, R cerebellum, and R putamen (time); bilateral middle temporal, R inferior frontal and R postcentral (group-time)
Qian et al., 2019 (B) *	delusions	30 AD, 15 delusions and 15 without	cross-sectional	fMRI, not specified	functional resting-state network differences between Alzheimer's disease (AD) patients with and without delusions	presence of hallucinations in non-delusional sample	DMN, clusters in MNI space	p=.005, voxel-wise followed by cluster size thresholding, minimum cluster size at an adjusted p=0.05, multiple comparisons	reduced connectivity within the DMN, significant cluster corresponded to the L IPL (including the angular gyrus); L superior temporal, L inferior orbitofrontal and R medial orbitofrontal (with higher delusion severity)

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Ramusino et al., 2021	delusions (also psychotic cluster) **	48 AD, 7 FTD, 4 LBD, 9 VD, 6 Dem NOS, 26 MCI (% not specified)	cross-sectional	CT and MRI, ROI	biological correlates of NPS; their impact in different forms of cognitive impairment (MCI, AD, FTD, LBD, and VD); correlations between NPS and CSF biomarkers and cortical visual rating scales	age, gender, education, MMSE, diagnosis	MTA, PA, and GCA-F	*p*<.05 2-sided, (p-values between	higher GCA-F scores and positive correlation with R GCA-F scores
Reeves et al., 2009	delusions	23 late onset AD (LOAD), 7 delusions	cross-sectional	[11C]RAC PET, ROI	symptom domains delusions and apathy would be associated with striatal dopamine (D2) receptor function	age, gender and MMSE	ventral striatum, caudate and putamen subdivided along rostro-caudal axis and sensorimotor striatum	multiple comparison	striatal dopamine (D2/D3) receptor availability increased
Schroeter et al., 2020	delusions (Capgras)	1 AD Capgras; 42 healthy controls (MRI analysis)	case study over time	MRI and FDG-PET, VBM and ROI (MRI)	report a case of Capgras delusions in a patient with Posterior Cortical Atrophy	age; total intracranial volume	occipital and temporoparietal cortex, posterior cingulate gyrus, precuneus, middle frontal gyrus, frontal eye field	*p*<.005 uncorrected voxel, (FWE) p<.05 corrected cluster	brain atrophy in occipital and temporoparietal regions, more in the R hemisphere, R fusiform gyrus (baseline), and posterior cingulate gyrus, precuneus, R middle frontal gyrus, frontal eye field, L fusiform gyrus (follow-up); glucose hypometabolism bilaterally in parietooccipital cortex and in the R frontotemporal cortex at baseline
Serra et al., 2010 *	delusions**	27 AD, 20 % delusions (early AD), <20% (moderate AD); 19 a-MCI (5% delusions); 23 healthy controls	cross-sectional	MRI, VBM	associations between regional GM volumes and clinical impact of NPS	MMSE, age, years of formal education, gender; intracranial volume	no hypothesis	*p*<.05, correction for multiple comparisons at voxel level (FWE) uncorrected level (p<0.001, min cluster size of 10 voxels)	lower GM volume R hippocampus; uncorrected level R middle frontal gyrus, parietal operculum cortex and precuneus

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Shanks and Venneri, 2002	delusions (misidentification)	3 AD with delusions	case studies	SPECT, not specified	association between misidentifications with R sided brain dysfunction	not specified	not specified	not specified	perfusion deficit in R temporoparietal region, R parietal region and R frontoparietal region
Staekenborg et al., 2008	delusions**	111 AD, 5% delusions	cross-sectional	MRI, MTA atrophy and WMH	associations of NPS with MTA and WMH	age, gender, MMSE	MTA, and whole brain (for WMH)	not specified	no significant results
Staff et al., 1999 *	delusions	33 AD, 18 delusions, 15 without	cross-sectional	SPECT, ROI	consistent SPECT perfusion pattern characterising AD patient with single content specific delusions (compared to non-delusional AD patients)	not specified	R and L frontal, parietal, occipital, limbic, temporal lobes, and the cerebellum in addition to no a priori hypothesis	not specified	significant asymmetry (reduced uptake on the right compared to the left) in frontal and limbic regions
Staff et al., 2000	delusions (autobiographic)	45 AD, 10 delusions, 35 without	cross-sectional	SPECT, VB	compare AD patients with similar content-specific delusions and AD patients with no clinical history of delusions	MMSE	whole brain	$p<.01$ uncorrected (considered only clusters normally produced at $p<.05$ prob.)	hypoperfusion R frontal lobe
Starkstein et al., 1994	delusions (paranoid, hypochondrial, grandeur, Capgras, infidelity, Cotard)	45 AD, 16 delusions, 29 patients without delusions	cross-sectional	SPECT, ROI	differences in rCBF between AD patients with and without delusions	not specified	R and L frontal inferior (orbital) and superior (dorsal), temporal inferior and superior, parietal; basal ganglia, thalamus, and cerebellum, in Matsui and Hirano atlas	not specified	lower CBF in both L and R, inferior, and superior temporal lobes
Sultzer et al., 2003	delusions	25 AD, 13 delusions	cross-sectional	PET, ROI	relationship between delusional thoughts and regional cortical metabolism in patients with AD	age, age at onset of dementia, duration of dementia, and overall cognition; agitation; mean global cerebral metabolic rate	precentral, premotor, prefrontal, dorsolateral, frontal gyrus, operculum, frontal pole, anterior cingulate, lateral orbitofrontal, central and medial orbitofrontal, temporal gyrus, fusiform gyrus, temporal pole, parahippocampal gyrus, amygdala, hippocampus, and posterior hippocampal	$p=.05$, corrected for multiple comparisons (Bonferroni)	hypometabolism in R prefrontal cortex, superior dorsolateral area and inferior frontal pole, and hypermetabolism in the lateral orbitofrontal region; hypometabolism in R prefrontal regions, L prefrontal regions, and the bilateral anterior cingulate (with severity of delusions); hypermetabolism in the L middle temporal gyrus

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Sultzer et al., 2014 *	delusions (paranoid and/or misidentification)	88 patients with AD (28 with delusions and 60 without)	cross-sectional	FDG-PET, VB	clinical associations among delusions, memory deficits, and poor insight, explore neurobiological correlates for these symptoms, and identify shared mechanisms	DRS total, DRS memory subscale, MMSE, and NRS inaccurate insight scores	not specified, MNI space	p<.01, voxel-level (voxel clusters at the p<.05 level), corrected for the search volume in each analysis	lower cortical metabolic activity R lateral frontal (middle and inferior frontal gyrus), orbitofrontal cortex, and bilateral temporal cortex (majority of middle and inferior temporal gyri and mid-portion of parahippocampal gyrus), bilaterally; R temporal cortex at corrected cluster level (with DRS as covariate); L inferior parietal lobule (patients with combined delusions compared to only paranoid)
Tagawa et al., 2014	delusions (persecutory)	31 AD patients (13 with delusions)	cross-sectional	MRI, VBM	relationship between MTA and persecutory delusions in patients with AD	total scores of the HDS-R and MMSE	MTA of the entire region of the entorhinal cortex, hippocampus, and amygdala	p<.05 (2-tailed)	R MTA is associated with persecutory delusions in patients with DAT
Tascone et al., 2017	delusions**	19 AD, 6 delusions; 13 healthy controls	cross-sectional	MRI, VBM and ROI	association between NPS and volume loss in brain regions involved in memory, emotional processing, and salience brain networks	total intracranial volume	whole brain, and prefrontal, lateral temporal and parietal cortices, anterior cingulate gyrus, temporo-limbic structures, and insula	p<.001, uncorrected for multiple comparisons (cluster size 25)	no significant results
Tetreault et al., 2020	delusions**	39 AD patients with delusions and 121 without	cross-sectional	MRI, atrophy network mapping	test if NPS in AD patients map onto specific brain networks	atrophy threshold, spatial extent of atrophy across subjects, hippocampal volume	atrophy network mapping in MNI space	p<.05 at a voxel-wise FWE	network identified in bilateral ventrolateral frontal, orbitofrontal frontal, and superior frontal cortices
Ting et al., 2015 *	delusions	58 AD, 29 with delusions and 29 without	cross-sectional	MRI, VBM	more pronounced grey matter atrophy in the R frontal lobe compared with matched patients without delusions, in a-MCI or AD patients	age; total intracranial volume	not specified, Talairach space	threshold p<.001 uncorrected (one-tailed); thresholding with FWE correction (Random Field Theory), and FDR correction at p<.05	greater R fronto-temporal grey matter atrophy in R insula, R precentral gyrus, L middle occipital gyrus (biggest); L middle frontal gyrus, R middle frontal gyrus, R inferior frontal gyrus, L cingulate gyrus, R middle frontal gyrus, R interior and superior frontal gyrus, R cerebellar decline, L postcentral gyrus, L middle frontal gyrus

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Tissot et al., 2021	delusions**	26 AD, 52 MCI (% of delusions not specified); 143 CU	cross-sectional	amyloid-PET, VB	increase of NPS emergence and severity and biomarkers of Aβ, tau, and in vivo neurodegeneration	gender, age, years of education and diagnosis	not specified	RFT correction	[18F]MK6240 uptake in the occipital/cuneus region (lower glucose metabolism)
Venneri et al., 2000	delusions	12 AD, 2 delusions, 10 without	case study over time	SPECT, ROI	neuroimaging profile of two patients with probable AD dementia	MMSE	R and L frontal, the R and L parietal and the occipital regions, cerebellum	not specified	blood flow reduction in the R prefrontal regions; lesions of the frontal lobes and of the R hemisphere
Whitehead et al., 2012	delusions (paranoid)	113 AD, 23 delusions (17 females) and 90 without (59 females)	cross-sectional	MRI, ROI	association of paranoid delusions, with regional cortical thickness and subcortical volume in AD	age, gender, education, age of onset or disease duration and ADAS-Cog; TIV	frontal pole, lateral and medial orbitofrontal, superior, and rostral middle frontal, superior, middle, and inferior temporal, and subcortical regions (caudate, putamen, nucleus accumbens and pallidum)	corrected for multiple comparisons; significant at the $p<.001$	whole sample: thinner L medial orbitofrontal and superior temporal cortex (not significant after controlling for cognitive status); in females only: L medial orbitofrontal and superior temporal regions

Notes. In the participants' column, the first sample size provided is the total number of participants with AD and/or MCI (inclusive of non-delusional controls; if healthy controls are also included, these are reported at the end of the cell); where the symptom of interest was present in a smaller ratio of this, this is specified consequently (as numbers or percentages, as available in the study); assessment tools such as MMSE and CDR are only reported in the confounding factors where these were specifically included in the analyses, while complete neuropsychological assessment was not reported in this table; unless differently stated, the full neuropsychiatric profile of the sample was not available (e.g., unknown if the participants presenting with delusions also presented with other symptoms); findings of the studies are only reported in relation to the symptoms investigated (i.e. delusions); all groups (sample with symptom of interest and control group) were used in the analyses which resulted in reported findings, unless differently stated; findings are only reported for the symptom of interest, therefore no significant findings only refers to that. *Abbreviations*. CIS=central insular sulcus, CFT=category fluency test, DLPFC=dorsolateral prefrontal cortex, FDR=false discovery rate, FWE=family wise error, FTD=frontotemporal dementia, GCA-F=global cortical atrophy-frontal, LBD=Lewy body dementia, LFT=letter fluency test,, MTA=medial temporal lobe atrophy, NOS=not otherwise specified (dementia), PA=posterior atrophy, rCBF=regional blood flow, rel-CBF=relative regional cerebral blood flow, rCMRglc=regional cerebral metabolic rate of glucose, SVD=small vessel disease, VaD/VD=vascular dementia, TIV=total intracranial volume; WTH=width temporal horn. *These studies were included in the meta-analysis. **These studies performed investigations on the other neuropsychiatric symptoms as well. ***These studies included investigations on hallucinations, and/or psychotic cluster.

In the four cross-sectional studies, Serra et al. (2010) found an association between delusions and the right hippocampus; similarly, Tagawa et al. (2014) demonstrated a link to right medial temporal atrophy, while Ting et al. (2015) reported greater right fronto-temporal grey matter atrophy, as well as in the right insula, right precentral gyrus, left middle occipital gyrus. Bruen et al. (2008) mainly found frontal involvement (right frontoparietal cortex and left frontal lobe) and the left claustrum. Lastly, a case study (Jedidi et al., 2015) reported atrophy in the posterior cingulate cortex, and the precuneus.

3.4.4.2. Grey matter atrophy: results from MRI – ROI Approach

The other common technique employed with MRI to investigate associated brain areas was using a region of interest (ROI) approach: here, results are averaged within each ROI to produce single metrics (e.g., grey matter volume, or cortical thickness), and it is normally used to test predetermined hypotheses. One longitudinal study reported the case of a person with posterior cortical atrophy who later developed Capgras syndrome (Schroeter et al., 2020): compared to a group of forty-two healthy control participants, greater involvement of the occipital and tempo-parietal regions, more in the right hemisphere, and right fusiform gyrus was reported at baseline, while the posterior cingulate gyrus, precuneus, right middle frontal gyrus, frontal eye field and left fusiform gyrus presented greater atrophy at follow-up, once the symptoms of misidentification were present. One study (Nowrangi et al., 2021), found associations between delusions and the left anterior cingulate cortex in severe and mild disease-severity groups, and the right subcallosal region in the mild subgroup only. In the last one (Whitehead et al., 2012), significant findings were found only in females, in the left medial orbitofrontal and superior temporal regions.

One study (Tetreault et al., 2020) used a new technique called ‘atrophy network mapping’, to identify a delusion network that included regions in the bilateral ventrolateral frontal, orbitofrontal frontal, and superior frontal cortices, which are consistent with brain regions previously identified (Aharon-Peretz et al., 1999; Boublay et al., 2020; Nakaaki et al., 2013b; Qian et al., 2019a; Schroeter et al., 2020; Ting et al., 2015; Whitehead et al., 2012).

3.4.4.3. Grey matter atrophy: results from CT

Grey matter atrophy was also investigated in two CT studies: one a case study (Förstl et al., 1991), which identified frontal lobe atrophy in relation to the presence of delusion of misidentification, and the other one found greater right involvement of the temporal lobe regions in a sample of participants presenting with paranoid and theft delusions (Geroldi et al., 2000).

3.4.4.4. Hypo and hyper perfusion measured with SPECT

Among the studies that investigated neuroanatomical correlates of delusions using SPECT, some explored delusions in general, while others explored the correlates of the different subtypes of delusions.

Concerning delusions in general, associated regions of hypoperfusion were the bilateral frontal gyri (Kotrla et al., 1995; Nakano et al., 2005; Staff et al., 2000), right prefrontal regions (Nakano et al., 2005; Venneri et al., 2000), right insula (Matsuoka et al., 2010), and right temporal areas (Nakano et al., 2005; Shanks & Venneri, 2002), as well as an overall asymmetry implicating the right hemisphere (Staff et al., 1999). One study (Pontón et al., 1995) also identified hyperperfusion in the superior (bilateral) and inferior (right) temporal gyri, and Brodmann's area 19 of the occipital lobe.

Delusions of theft were associated with hypoperfusion in the right medial posterior parietal region (Fukuhara et al., 2001), right inferior temporal gyrus (Nakatsuka et al., 2013), bilateral anterior cingulate cortex (Nakano et al., 2005), left and right thalamus and left posterior cingulate gyrus, in addition to hyperperfusion in the left inferior frontal gyrus and left anterior cingulate gyrus (Nomura et al., 2012).

Persecutory delusions were linked to hypoperfusion in the right and left precuneus, and hyperperfusion in the left insula and right thalamus (Nomura et al., 2012).

In association with delusions of abandonment, hypoperfusion was identified in the right parahippocampal gyrus, right posterior insula (Nakatsuka et al., 2013), right inferior temporal gyrus, left insula, left middle frontal gyrus, left putamen and left posterior cingulate gyrus (Nomura et al., 2012).

Lastly, misidentification was associated with hypoperfusion in the right amygdala (Nakatsuka et al., 2013), left lingual gyrus, right middle occipital gyrus (Nakano et al., 2005) and right middle temporal gyrus, and hyperperfusion in the left medial frontal gyrus and left precentral gyrus (Nomura et al., 2012).

3.4.4.5. Hypo and hyper metabolism measured with PET

18F-FDG PET imaging was most commonly employed to study regional cortical metabolism in association with delusions. Three studies assessed their hypotheses using ROIs, and despite having comparable designs, they reported some similar, along with some contrasting findings, when analysing patterns of hypo and hyper metabolism. Focusing first on hypometabolism, this was linked to the presence of delusions as identified by Hirono et al. (1998) in the left medial occipital region, whereas Sultzer et al. (2003) noted associations in the right prefrontal cortex, the superior dorsolateral area and inferior frontal pole, in addition to severity of delusions with prefrontal regions and the anterior cingulate cortex. Hypometabolism in this last region was also found by Mentis et al. (1995), as well as orbitofrontal areas (bilaterally), and the left posterior medial temporal area. Conversely, there were also temporal and orbitofrontal areas that were identified as hypermetabolic: the first by all three studies, while the second was found only by Sultzer et al. (2003).

In 2014, Sultzer et al. instead applied voxel-based (VB) whole-brain analyses, and somewhat similarly to previously mentioned studies, they found hypometabolism, in the right middle and inferior frontal gyrus, orbitofrontal cortex, and bilateral temporal cortex (which included the majority of the middle and inferior temporal gyri and the mid-portion of the parahippocampal gyrus).

Two case studies of patients with Capgras syndrome reported different regions of hypometabolism: the first implicating the right frontotemporal cortex and parietooccipital cortex (Schroeter et al., 2020), while the second highlighted the left dorsal posterior medial prefrontal cortex (MPFC), upper left precuneus, posterior cingulate cortex and inferior temporal lobe (Jedidi et al., 2015).

Lastly, one study used which used [18F]MK6240-tau-PET (Tissot et al., 2021), found that those with delusions showed higher cuneus and occipital uptake, and another (Reeves

et al., 2009) found an association between delusions and an increase in striatal dopamine (D2/D3) receptor availability, using [11C]raclopride (RAC) PET.

3.4.4.6. Use of MRI to study changes in the white matter and WMH

Four studies investigated changes in the white matter, in association with delusions (Lee et al., 2006; Nakaaki et al., 2013a; Ogawa et al., 2013; Palmqvist et al., 2011). Employing diffusion tensor imaging to investigate white matter abnormalities, Nakaaki et al. (2013a) identified abnormalities in white matter integrity, localised mainly in the parieto-occipital region, and to a lesser extent in the body of the corpus callosum and superior temporal gyrus white matter.

Lee et al. (2006) and Palmqvist et al. (2011) employed the Age-Related White Matter Changes scale in association with delusions: they both identified a relationship with the left basal ganglia (however in Lee and colleagues' analysis this was associated only with delusions of misidentification), alongside changes in the bilateral frontal and left parietooccipital white matter. Lee et al. (2006) also found left frontal white matter changes in association with Capgras syndrome, bilateral frontal and parieto-occipital white matter changes with phantom boarder, and right basal ganglia in association with the belief that a dead person is still alive.

Magnetic resonance imaging has also been employed to identify the presence of lesions in the white matter, or white matter hyperintensities (WMH), which show up as areas of increased brightness when visualised by T2-weighted MRI. In relation to delusions, Anor and colleagues found significant associations with delusions in the right frontal lobe (Anor et al., 2017), and for the summative whole brain measure (Anor et al., 2021). In Ogawa et al. (2013), who investigated cerebral small vessel disease (the progression of which is directly associated with the presence of WMH (Xia et al., 2020)) an association was found between this and the presence of delusions.

3.4.4.7. Recent applications of fMRI

A recent study identified differences in resting state fMRI functional connectivity in delusional compared to non-delusional patients (Qian et al., 2019b), with a significant cluster of lower functional connectivity corresponding to the left inferior parietal lobule

within the default mode network. Higher delusion severity was also found to be linked to significantly weaker connectivity in the left superior temporal, left inferior orbitofrontal and right medial orbitofrontal cortex.

3.4.5. Hallucinations

Results are summarised in Table 3.3.

3.4.5.1. Grey matter atrophy: results from MRI

Grey matter atrophy in association with hallucinations was reported by four studies. A longitudinal, ROI study (Donovan et al., 2014) identified an association with lower baseline supramarginal cortical thickness of the lateral parietal cortex and the future development of hallucinations.

Two studies employed voxel-based morphometry, and reported similarities in the impairment of temporal and frontal areas. Specifically, Blanc et al. (2014) found atrophy in the anterior part of the right insular cortex and a discrete part of the left superior frontal gyrus in association with the presence of hallucinations, and in the right anterior part of the insula, right precentral gyrus and right superior temporal gyrus in association with hallucination intensity. Boublay et al. (2020) found associations with the middle and inferior frontal gyri bilaterally, the right anterior cingulate cortex, right orbitofrontal cortex, left superior medial gyrus, left middle temporal gyrus, right thalamus, and right caudate nucleus.

Holroyd et al. (2000) found a decreased ratio of measured occipital volume to whole brain volume.

3.4.5.2. Hypo and hyper perfusion measured with SPECT

Mori et al. (2006) presented a case study of musical hallucinations, highlighting lower blood flow in the left superior temporal gyrus, and left angular gyrus.

Table 3.3

Studies on Hallucinations

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Anor et al., 2017	hallucinations **	67 AD, 10.3% hallucinations, 38 mixed AD/VaD 18.8% hallucinations	cross-sectional	MRI, WMH	differences in incidence of NPS, in relation to frontal WMH volume	age	frontal lobe, in Atlas of the Human Brain	$p<.05$	no significant results
Anor et al., 2021	hallucinations **	138 AD, 114 MCI-AD, from 2 to 8.5% incidence hallucinations	cross-sectional and longitudinal (at 1 year)	MRI, WMH	relationship between NPS, and WMH burden in MCI-AD or AD patients; relationship between WMH volume and future development of NPS	use of psychotropic medications; total volumes of MRI scans normalised for head size	load of WMH on whole brain	FDR to correct for multiple comparison	whole brain WHM load (future hallucinations severity sub-scores)
Berlow et al., 2010	hallucinations **	37 AD, 10 hallucinations	cross-sectional	MRI, WMH, VBM	association between NPS and volumetric reduction of grey matter (of the whole brain and hippocampus) and increase of WMH	age and MMSE, skull size	whole brain and hippocampus	$p<.10$	no significant results

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Blanc et al., 2014	hallucinations	39 AD hallucinations, 39 without; 39 healthy elderly controls (MRI); 19 AD with hallucinations, 20 without; 20 healthy elderly controls (PET)	cross-sectional	MRI and FDG-PET, VBM (MRI), VB (PET)	posterior (occipital) and anterior (frontal) atrophy and hypometabolism in association with hallucinations (presence and intensity)	age: total amount of grey matter (MRI), mean brain metabolism	occipital and frontal lobe, in MNI space	$p<.001$ uncorrected, minimum cluster size of 25 voxels	WM atrophy in lingual gyri of the occipital lobe, GM atrophy in anterior R insular cortex, L superior frontal gyrus (presence); WM atrophy in L precuneus and GM atrophy in R anterior insula, R precentral gyrus and R superior temporal gyrus (intensity); hypometabolism in R frontal lobe and hypermetabolism L superior frontal gyrus, fusiform gyrus, post-central gyrus, super marginal gyrus and precuneus (presence); hypometabolism in L limbic lobe, cingulate gyrus and R pre-central gyrus (intensity); hypermetabolism in L superior frontal gyrus, L fusiform gyrus, L post-central gyrus, L supramarginal gyrus and L precuneus (presence)
Boublay et al., 2020	hallucinations **	53 AD, 2 hallucinations; 40 healthy controls	longitudinal	MRI, VBM	regional brain volumes of the whole brain in association with behavioural changes at the mild stages of AD	gender, age; type of MRI	whole brain, transformed to Montreal Neurological Institute (MNI) space	$p\leq.001$	R middle frontal gyrus, R anterior cingulate cortex, R orbitofrontal cortex, L superior medial gyrus, L middle temporal gyrus, R thalamus, R caudate nucleus and L inferior frontal gyrus
Donovan et al., 2014	hallucinations (also apathy)	188 AD dementia (5.3% hallucinations), 395 MCI (0.3 % hallucinations), 229 CN (0.4 % hallucinations)	longitudinal	MRI, ROI	relations of MRI cortical thickness, with apathy and hallucinations	diagnosis, gender, age Apo-E genotype, premorbid intelligence, memory performance, processing speed, antidepressant use, AD duration, baseline dependent variable	bilateral rostral anterior cingulate, inferior temporal, medial orbitofrontal and supramarginal cortices, bilateral lingual, rostral middle frontal and superior parietal cortices	$p<.01$ corrected for multiple comparison (Bonferroni)	supramarginal cortical thickness (baseline, with greater rate of increase over time)

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
García-Alberca et al., 2019	hallucinations **	46 AD, 7 hallucinations	cross-sectional	MRI, atrophy and WMH	relationship between WMH and medial temporal lobe atrophy (MTA) observed on MRI and specific NPS in patients with AD	age, gender, education, duration of disease, diabetes mellitus, hypertension, hyperlipidaemia, heart disease, MMSE, CFT, LFT	WMH in frontal, occipital, lateral periventricular, frontal parietal, temporal and occipital deep subcortical, basal ganglia, infratentorial lesions; L and R MTA volumes	p<.05	no significant results
Hirono et al., 1998	hallucinations (mainly visual) ***	26 AD, 7 hallucinations, 39 without	cross-sectional	FDG-PET, ROI	AD patients with delusions present distinct features in regional cerebral metabolism	mean value of all cortical metabolic rates for glucose	dorsolateral and basal prefrontal, anterior cingulate, superior, medial, middle inferior temporal, medial and lateral occipital, inferior parietal; in Talairach and Tournoux atlas	*p*<.05 corrected for multiple comparison (Bonferroni)	no significant results
Holroyd, Shepherd, and Downs, 2000	hallucinations (visual)	14 AD, 7 with hallucinations and 7 without	cross-sectional	MRI, voxels	more neuropathology of occipital cortex in AD patients with visual hallucinations	MMSE (match controls at same cognitive score); participants brain sizes	whole brain and regions	not specified	decreased ratio of measured occipital volume to whole brain volume
Hořínek et al., 2006	hallucinations **	30 AD, 7% hallucinations	cross-sectional	MRI, ROI	association between the reduction of amygdala volume in AD and psychiatric symptoms	age, gender, and level of education; intracranial and total brain volumes	amygdala and hippocampus	*p*<.05	no significant results

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Jaramillo-Jimenez et al., 2021	hallucinations **	55 AD patients, 34 dementia Lewy Body, 12.2% hallucinations (Year 2)	longitudinal (baseline, Years 1,2,3,4,5)	MRI, not specified	association between amygdala volumes and the longitudinal development of NPS in AD and DLB	gender, diagnosis and MMSE total score, time in study; intracranial volume (head size and gender differences), centre of MRI acquisition	amygdala	p<.05 corrected for multiple testing (FDR)	no significant results
Lee et al., 2006	hallucinations **	55 AD, 10 with psychosis (% hallucinations not specified)	cross-sectional	MRI, White Matter Changes (Age-Related WMC scale)	relationship between white matter changes seen on MRI and neuropsychiatric symptoms in probable AD	age, education, gender, and duration of illness	L and R frontal areas, L and R parieto-occipital areas, L and R temporal areas, L and R basal ganglia	p<.05 uncorrected	no significant results
Lin, Yu and Pai, 2006	hallucinations (visual)	10 AD, 5 hallucinations, 5 without	cross-sectional	MRI, WMH	relationship between occipital white matter lesions (PVHs and DWHs), and visual hallucinations	not specified	not specified	p<.05	increased occipital PVHs and an absence of occipital DWHs
Lopez et al., 2001	hallucinations ***	9 AD, 2 hallucinations, 2 delusions, 5 no psychotic symptoms; 9 elderly controls	cross-sectional	PET, ROI	critical brain region that serves as a common denominator for the development of psychosis	not specified	orbitofrontal, frontal dorsolateral, anterior cingulate, medial temporal, superior temporal, parietal, occipital cortex, basal ganglia, and thalami	not specified	lower rel-CBF in R parietal cortex
Moon et al., 2014	hallucinations **	40 AD, 4 with hallucinations	cross-sectional	MRI, ROI	association between the volume ratio of the insular cortex and neuropsychiatric symptoms in patients with AD	age, CDR score, vascular risk factor and other NPS; WMH, total grey matter volume divided by other NPS, intracranial volume	insular cortex, subdivided into four subregions by the CIS and bilaterally: the R anterior insular cortex, R posterior insular cortex, L anterior insular cortex and L posterior insular cortex	not specified	no significant results

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Mori et al., 2006	hallucinations (musical)	747 AD, 1 hallucinations	case-study	SPECT, not specified	regions related to musical hallucinations	not specified	not specified, in Talairach and Tournoux atlas	p<.001 uncorrected	increased rCBF in the L superior temporal gyrus, and L angular gyrus
Ogawa et al., 2013	hallucinations **	163 AD % hallucinations not specified	cross-sectional	MRI, WMH (Fazekas scale)	relationship of cerebral SVD observed on MRI with NPS	age, gender, years of education, duration of disease, cholinesterase inhibitor usage and CDR	not specified	p<.05 uncorrected	no significant results
Palmqvist et al., 2011	hallucinations **	258 AD, 10% hallucinations	cross-sectional	CT or MRI, White Matter Changes (Age-Related WMC scale)	independent association between regional subcortical lesions and NPS	cognitive ability, atrophy	frontal lobe anterior to the central sulcus, the parietooccipital area and the basal ganglia (striatum, globus pallidus, thalamus, internal and external capsules), and insula	entry limit was p=.05, limit of removal p=.051 (collinearity reduced by L and R regions entered separately)	lesions in the basal ganglia (increased risk of hallucinations)
Ramusino et al., 2021	hallucinations ***	48 AD, 7 FTD, 4 LBD, 9 VD, 6 Dem NOS, 26 MCI (% not specified)	cross-sectional	CT and MRI, ROI	biological correlates of NPS, evaluating their impact in different forms of cognitive impairment (MCI, AD, FTD, LBD, and VD), and correlations between NPS and CSF biomarkers and cortical visual rating scales	age, gender, education, MMSE, diagnosis	MTA, PA, and GCA-F	p<.05 2-sided, (p-values between 0.05 and 0.1 were also reported)	higher GCA-F scores
Serra et al., 2010	hallucinations **	27 AD, 10% hallucinations); 23 healthy controls	cross-sectional	MRI, VBM	associations between regional GM volumes and clinical impact of NPS	MMSE, age, years of formal education, gender; intracranial volume	no hypothesis	p<.05, correction for multiple comparisons at voxel level (FWE)	no significant results

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Staekenborg et al., 2008	hallucinations **	111 AD, 5% hallucinations	cross-sectional	MRI, MTA atrophy and WMH (Fazekas scale)	associations of NPS with MTA and WMH	age, gender, MMSE	MTA, and whole brain (for WMH)	not specified	no significant results
Tascone et al., 2017	hallucinations **	19 AD, 4 hallucinations; 13 controls	cross-sectional	MRI, VBM and ROI	association between NPS and volume loss in brain regions involved in memory, emotional processing, and salience brain networks	total intracranial volume	whole brain, and prefrontal, lateral temporal and parietal cortices, anterior cingulate gyrus, temporo-limbic structures, and insula	$p<.001$, uncorrected for multiple comparisons (cluster size 25 contiguous voxels)	no significant results
Tetreault et al., 2020	hallucinations **	39 AD patients with delusions and 121 without	cross-sectional	MRI, atrophy network mapping	test if NPS in AD patients map onto specific brain networks	atrophy threshold, spatial extent of atrophy across subjects, hippocampal volume	atrophy network mapping in MNI space	$p<.05$ voxel-wise FWE	no significant results
Tissot et al., 2021	hallucinations **	26 AD, 52 MCI and 143 CN (% hallucinations not specified)	cross-sectional	amyloid-PET, VB	relationship between increase of NPS, and in vivo neurodegeneration	gender, age, years of education and diagnosis	not specified	RFT correction	[18F]MK6240 uptake in the medial occipital cortex (lower glucose metabolism)
Wang et al., 2021	hallucinations **	22 AD, 3 hallucinations)	cross-sectional	MRI, regions	correlation between amygdala atrophy and clinical features of AD	not specified	amygdala	$p<.05$	more serious amygdala atrophy (however no significant correlation)

Notes. In the participants' column, the first sample size provided is the total number of participants with AD and/or MCI (inclusive of non-hallucinations controls; if healthy controls are also included, these are reported at the end of the cell); where the symptom of interest was present in a smaller ratio of this, this is specified consequently (as numbers or percentages, as available in the study); assessment tools such as MMSE and CDR are only reported in the confounding factors where these were specifically included in the analyses, while complete neuropsychological assessment was not reported in this table; unless differently stated, the neuropsychiatric picture for the sample of interest was not available (e.g., unknown if the participants presenting with delusions

also presented with other symptoms); findings of the studies are only reported in relation to the symptoms investigated (i.e. hallucinations); all groups (sample with symptom of interest and control group) were used in the analyses which resulted in reported findings, unless differently stated; findings are only reported for the symptom of interest, therefore no significant findings only refers to that (i.e. the study might have other significant findings with respect to other NPS that are not reported here).

Abbreviations. CIS= central insular sulcus, CFT=category fluency test, DLPFC=dorsolateral prefrontal cortex, CN=cognitively normal, FDR=false discovery rate, FWE=family wise error, FTD=frontotemporal dementia, GCA-F=global cortical atrophy-frontal, LBD=Lewy body dementia, LFT=letter fluency test, MTA=medial temporal lobe atrophy, NOS=not otherwise specified (dementia), PA=posterior atrophy, rCBF=regional blood flow, rel-CBF=relative regional cerebral blood flow, rCMRglc=regional cerebral metabolic rate of glucose, VaD/VD=vascular dementia

**These studies performed investigations on other neuropsychiatric symptoms as well

***These studies included investigations on delusions, and/or psychotic cluster

3.4.5.3. Hypo and hyper metabolism measured with PET

One key study on the presence and intensity of hallucinations that was mentioned above Blanc et al. (2014) also made use of the corresponding FDG-PET data from a subset of the participants, and identified: hypometabolism in the right frontal lobe with the presence, and in the left limbic lobe, cingulate gyrus and right pre-central gyrus with the intensity. Hypermetabolism was instead associated with the presence of hallucinations in the left hemisphere, particularly in the superior frontal gyrus, fusiform gyrus, post-central gyrus, supramarginal gyrus and precuneus. Lopez et al. (2001) found frontal, temporal, and right parietal cortex hypoperfusion in association with the presence of hallucinations in their AD patient sample. Lastly, with the use of [18F]MK6240-tau-PET, Tissot et al. (2021) identified uptake in the medial occipital cortex in association with severity of hallucinations.

3.4.5.4. Use of MRI to study changes in the white matter and WMH

White matter atrophy was identified by Blanc et al. (2014) in the lingual gyri of the occipital lobe, in association with the presence of hallucinations, and in the left precuneus with hallucination intensity. An alternative study that investigated the presence of WMH in association with hallucination severity Anor et al. (2021) found a significant correlation with WMH load in the entire brain.

Lin et al. (2006) found an association between the presence of visual hallucinations and increased occipital periventricular hyperintensities, and an absence of occipital deep white matter hyperintensities.

3.4.6. Psychotic Cluster

Results are summarised in Table 3.4.

3.4.6.1. Grey matter atrophy: results from MRI

Ten studies investigated psychosis as a cluster using MRI, of which eight used the ROI technique to study regional differences in grey matter.

Table 3.4.

Studies on Psychotic Cluster

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Balthazar et al., 2014	psychosis **	20 AD, 10% with delusions and 10% hallucinations; 17 healthy controls	cross-sectional	fMRI, functional ROIs	alterations in functional networks (default-mode and salience) in relation to NPS clusters	grey matter atrophy	dorsal and ventral DMN and anterior and posterior SN	$p<.01$, FDR correction	no significant results
Banno et al., 2014	psychosis	32 AD, % of psychosis not specified	cross-sectional	SPECT, voxel-by-voxel	relationship between rCBF and presence of psychosis (as one dimension of agitated behaviour)	age, gender, years of education, duration of illness, MMSE scores	not specified	$p<.05$, FDR correction, cluster extent thresholds at 100 voxels to reduce noise	lower rCBF values in the R angular gyrus and the R occipital lobe
Barber et al., 1999	psychosis (delusions and visual hallucinations)	28 AD, 25 VaD, 27 LBD, 34 delusions, 29 hallucinations; 26 controls	cross-sectional	MRI, WMH	relation of white matter changes on MRI in patients with AD (and also vascular dementia, and dementia with Lewy bodies), with non-cognitive features	not specified	WMH rated in frontal, temporal, parietal, occipital, and basal ganglia regions	$p<.01$ and $p<.05$	absence of occipital WMHs (analyses carried out on overall sample: all types of dementia together)
Cappelletto et al., 2021	psychotic symptoms **	17 AD with NPS, 14 NPS developers % of psychosis not specified, 29 without	longitudinal	FDG-PET, VB	common metabolic pattern of positive NPS and to explore whether such a pattern could have a role in predicting their onset	age and MMSE	not specified; in Talairach and Tournoux atlas	$p<.001$ uncorrected	association between brain hypometabolism in the temporal cortex and positive NPS
D'Antonio et al., 2019	psychosis (misidentificati on and paranoia)	17 AD with psychosis and 15 without	longitudinal, 2-year interval	MRI, VBM	detecting what grey matter alterations, their location, and the rate of atrophy are associated with psychosis of AD	time from AD onset; total intracranial volume	whole brain	$p<.05$, FWE corrected at cluster level; $p<.001$ uncorrected at peak level	smaller volume in R anterior-inferior temporal lobe, extending to fusiform gyrus; trend towards significance for the Group-by-Time interaction in R anterior insula; greater atrophy in ventral-anterior temporal lobe (misidentification subtype)

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
D'Antonio et al., 2021	psychosis (misidentification and paranoia)	17 AD with psychosis, 15 without psychosis	cross-sectional	MRI, ROI, RBM	regional FD in association with psychosis; misidentification associated with alterations in ventral visual stream regions, and paranoia with frontal and temporal regions	general cognitive decline (ADAS-Cog score) and time elapsed between NPI administration; MRI acquisition	primary and early visual cortex, dorsal and ventral visual stream, middle temporal area, medial temporal cortex, anterior cingulate and medial prefrontal cortex, orbital and polar frontal cortex, and dorsolateral prefrontal cortex	p=.001, Bonferroni multiple comparisons	reduced cortical complexity in the R ventromedial visual cortex (psychosis compared to control); decreased cortical complexity in the R entorhinal cortex (misidentification)
Hayata et al., 2015	psychosis, including sleep **	33 AD, % of psychosis not specified; 29 controls	cross-sectional	MRI, not specified	correlations between neuroanatomical structures with NPS	age, gender, and education level	not specified, in Talairach and Tournoux atlas	FDR corrected	no significant results
Jeong et al., 2021	psychosis	172 a-MCI, of which 94 progressed to AD and 18 to AD+P, at follow-up	longitudinal	MRI, ROI	effect of sub-regional thickness in the frontal lobe on the risk of AD+P conversion in patients with aMCI, association independent of hippocampal atrophy	age, gender, education level, follow-up period; total brain volume, hippocampal volume	frontal lobe, specifically anterior cingulate cortex (rostral and caudal ACC)	p<.05; Bonferroni multiple comparisons (continuous variables), chi-square (discrete variables)	thinner L caudal anterior cingulate cortex (cACC) compared (psychosis converters compared to aMCI stable or AD converters); decreasing trend in both biltaeral rostral ACC and R cACC (did not reach significance)
Koppel et al., 2014	psychosis	21 AD with psychosis and 21 without (trait analysis), 39 AD patients with psychosis and 39 without (state analysis)	longitudinal	FDG-PET, CMRgl by sROI	perturbations in frontal brain glucose metabolism associated with psychosis, preceding it (“trait” effect) or coincide with the psychotic “state”	trait and state psychosis definition, age-matched controls	L and R angular gyrus, bilateral posterior cingulate gyrus, L and R inferior temporal gyrus, orbitofrontal region, in MNI space	p<.05 uncorrected	decrement in mean brain CMRgl for each ROI in the AD+P compared with AD-P; only orbitofrontal impairment robust enough to achieve statistical significance (focal frontal vulnerability as a mediator of progression)

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Lee et al., 2019	psychosis	26 AD with psychosis, 48 AD without psychosis	cross-sectional	MRI, ROI	regionally distributed MTC thickness (or hippocampal volume) and frontal lobe volume are independently associated with the onset of AD with psychosis	age, gender, years of education, CDR-SOB score, MMSE (K-version), duration of AD; total intra-cranial and total frontal volume	total frontal cortex, total temporal cortex, and subregions of the medial temporal cortex (HC, entorhinal, and parahippocampus), in the Desikan-Killiany Atlas	$p<.05$	R hippocampal atrophy (adjusted for frontal volume)
Lee et al., 2021	psychosis	27 AD with psychosis	longitudinal (3-months intervals)	MRI, ROI	effect of decreased cortical thickness or volume of medial temporal lobe structures on the risk of incident psychosis in AD patients	age, gender, education level, CDR-SOB score, follow up period; total intracranial volume	regions of interest were structures of the medial temporal cortex (the hippocampus, entorhinal, and parahippocampus) included in the Desikan-Killiany Atlas	$p<.05$	L and R hippocampal volume, L and R entorhinal cortical thickness, L and R parahippocampal volume
Lee et al., 2016	psychosis (misidentification and paranoid)	40 AD with psychosis, 25 without	cross-sectional	MRI, VBM	association between brain regional grey matter volume and two subtypes of psychotic symptoms, paranoid and misidentification, in antipsychotic-naïve mild or moderate AD patients	age, gender, education, CDR score and K-NPI non-psychotic scores; total intracranial volume	not specified, in MNI template	$p<.001$ uncorrected at voxel level, threshold of contiguous 100 voxels	R inferior parietal lobule, R lingual gyrus, L cuneus, R middle frontal gyrus, R superior occipital gyrus R middle temporal gyrus (misidentification); R middle frontal gyrus, R medial frontal gyrus, L middle frontal gyrus, L medial frontal gyrus, L superior frontal gyrus, L inferior frontal gyrus, R middle occipital gyrus, R superior frontal gyrus, R middle temporal gyrus (misidentification vs paranoia); R medial frontal gyrus, L inferior frontal gyrus, L middle temporal gyrus, L medial frontal gyrus, R middle frontal gyrus, L cuneus, L middle frontal gyrus, R superior frontal gyrus, L lingual gyrus (paranoia)
Lee, Kim, and Lee, 2020	psychosis **	70 AD, % psychosis not specified	cross-sectional	fMRI, DMN	relationship between NPS subsyndromes and resting functional connectivity (DMN) in patients with Alzheimer's disease	not specified	anterior and posterior DMN	clusters based on FWE corrected $p<.05$, cluster-determining threshold at uncorrected $p<.001$	no significant results

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Lopez et al., 2001	psychosis	9 AD, 2 delusions, 2 hallucinations and 5 without; 9 elderly controls	cross-sectional	PET, ROI	critical brain region that serves as a common denominator for the development of psychotic phenomenon in AD	not specified	orbitofrontal, frontal dorsolateral, anterior cingulate, medial temporal, superior temporal, parietal and occipital cortices, and basal ganglia and thalami	not specified	lower rel-CBF in the L medial temporal and dorsolateral frontal cortices
Makovak et al., 2016	psychosis **	58 AD, % of psychosis not specified	cross-sectional	MRI, VBM	correlations between regional GM atrophy and WM abnormalities in the corpus callosum (CC) of AD patients with NPS	individual brain size	corpus callosum, in MNI standard space	$p<.05$	MD and FA in the genu of the CC, and GM atrophy in the fronto-orbital cortex, R anterior cingulate cortex (paracingulate) and R thalamus
McLachlan et al., 2018	psychosis (misidentification and paranoia)	104 AD patients (47 with psychosis and 57 without)	cross-sectional	MRI, ROI	psychosis associated with visuo-perceptual/frontal networks, and regional brain volume differences in relation with paranoia (persecutory delusions) or misidentification (misidentification delusions and/or hallucinations)	age, duration of illness, ADAS-Cog; total intracranial volume	entorhinal cortex, parahippocampal gyrus, lateral occipital cortex, fusiform gyrus, lingual gyrus, rostral and caudal anterior cingulate cortex, rostral middle frontal gyrus and medial orbitofrontal cortex	$p<.05$	L parahippocampal gyrus and L lingual gyrus; L and R parahippocampal gyri and post-hoc pairwise comparisons showed significantly lower L parahippocampal volume in (misidentification and mixed groups); R parahippocampal volume (mixed group)
Mega et al., 2000	psychosis	20 AD patients (10 with psychosis, 10 without)	cross-sectional	SPECT, 6mm voxels (FWHM of the scanner) within ROI	functional imaging profile of patients with psychosis in AD	demographic profile and MMSE	not specified, in Talairach and Tournoux atlas	Bonferroni correction	L medial orbital frontal, L anterior cingulate, L dorsolateral frontal, L dorsolateral frontal, L dorsolateral parietal, L pulvinar, L ventral striatum, L cerebellum, R dorsolateral frontal, R dorsolateral frontal, R medial frontal
Misquitta et al., 2020	psychosis **	121 AD, 315 MCI, % of psychosis not specified; 225 healthy controls	longitudinal	MRI, WMH and ROI	WMH burden and regional GM atrophy contribution to NPS (over time)	age, gender, cohort (control, MCI, or AD); mean GM in each ROI, WMH segmenting sequences modality	not specified, in MNI atlas	$p<.05$, corrected for multiple comparisons (FDR)	lower GM mean deformation-based morphometry values in the R middle temporal gyrus and L Heschl's gyrus, and R and L cerebellum; WMH load

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Moran et al., 2008	psychosis	157 AD, 79 with psychosis and 78 without	cross-sectional	SPECT, VB	determine if the presence of psychotic symptoms in patients with Alzheimer's disease is associated with abnormal regional cerebral function	age, MMSE	not specified	*p*<.05, corrected for multiple comparisons (FDR) at voxel level	hypoperfusion in R inferior-lateral prefrontal cortex and R mid-temporal cortex was observed among female AD patients with psychotic symptoms, but not among male patients; R striatal hyperperfusion among male AD patients with psychotic symptoms, but not among females (peak of this cluster centred at the border of the R posterior putamen and the globus pallidus)
Rafii et al., 2014	psychosis	389 MCI and AD, 47 with psychosis and 342 without	cross-sectional and longitudinal	MRI, ROI	relationship between regional neocortical atrophy and psychotic symptoms in adults MCI and AD	age, education, MMSE and ADAS-Cog	anterior cingulate, entorhinal, lateral frontal, lateral occipital, lateral parietal, medial orbitofrontal, and posterior cingulate	*p*<.05	volume loss in anterior cingulate, lateral frontal, lateral occipital, lateral parietal, medial orbitofrontal; greater lateral frontal, and lateral parietal atrophy at 1-year postbaseline in patients with psychotic symptoms and/or antipsychotic medication use (controlling for baseline ADAS-cog performance)
Ramusino et al., 2021	psychosis ***	48 AD, 7 FTD, 4 LBD, 9 VD, 6 Dem NOS, 26 MCI (% not specified)	cross-sectional	CT and MRI, ROI	biological correlates of NPS, impact in different forms of cognitive impairment (MCI, AD, FTD, LBD, and VD), and correlations NPS with CSF biomarkers and cortical visual rating scales	age, gender, education, MMSE, diagnosis	MTA, PA, and GCA-F	p<.05 2-sided, (p-values between 0.05 and 0.1 were also reported)	positive correlations with R GCA-F scores
Santhosh et al., 2009	psychosis	9 AD, 4 with psychosis and 5 without)	cross-sectional	[18F]deuteroaltanserinPET, ROI	correlations between regional 5-HT2A receptor binding and psychosis/depression in AD patients	age, gender	anterior cingulate, frontal, medial frontal, temporal, parietal, occipital, cerebellum, putamen, and thalamus	not specified	no significant results
Serra et al., 2018	psychosis **	84 AD, 48 a-MCI, 22 with psychosis; 37 healthy elderly controls	cross-sectional	fMRI, ROI	changes in VTA and LC connectivity (used as a proxy of neuronal loss) in relation with higher level of dysfunctions in AD	years of formal education; whole-brain GM volumes, MTA	PCC, right and left angular gyrus and whole brain (VTA connectivity)	*p*<.05 FWE corrected at cluster level	no significant results

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Serra et al., 2020	psychosis (including disinhibition) **	101 AD, 56 a-MCI, 31 with psychosis; 35 healthy elderly controls	cross-sectional	fMRI, ROI	alterations of functional brain connectivity at different clinical stages of AD patients, with NPS	MMSE score, age, gender, education, psychoactive medications; motion, clinical status, GM volumes, MTA	not specified	$p<.05$ Bonferroni correction	reduced connectivity in the R cingulum, hippocampus and insula, and in the bilateral supramarginal gyrus
Siafarikas et al., 2021	psychosis **	133 AD, 102 MCI, % of psychosis not specified	cross-sectional	MRI, Regions	hypothesized NPS to be associated with the thickness and volume of frontotemporal regions, including the anterior cingulate cortex (ACC)	age, gender, and diagnosis	not specified	$p<.005$ FDR correction	L post-central gyrus
Sultzer et al., 1995	psychosis **	21 AD, % psychosis not specified	cross-sectional	FDG-PET, ROI	psychiatric symptomatology associated with the extent of global cortical hypometabolism and relationships between specific symptoms and hypometabolism in individual cortical lobes	age, MMSE, NRS total score, duration of dementia	medial and lateral orbitofrontal, dorsomedial frontal, dorsolateral convexity, precentral gyrus, post-central gyrus, superior and inferior lobule, primary and secondary visual, superior, and inferior temporal, septal region, cingulate, hippocampus, para-hippocampal gyrus, temporal pole, insula	not specified	frontal cortex hypometabolism
Sultzer et al., 2002	psychosis **	18 AD patients (males), % with delusions not specified	cross-sectional	MRI, WMH	extent of subcortical WMH (SH) related to the degree of regional cortical hypometabolism and severity of NPS	MMSE rank	not specified	not specified	trends of positive correlation between hyperintensities in the R and the anterior halves of the subcortex (non-significant after covarying for MMSE)

Author(s), Year	Symptom(s) Investigated	Participants (Total and Analyses of Interest)	Design(s)	Neuro-imaging Tech-niques/ Metrics	Aim(s) (in Relation to this Review)	Confounding Factors (Accounted for in the Analyses)	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Yasuno, Minami and Hattori, 2020	psychosis (including sleep) **	21 AD, 29 MCI, % of psychosis not specified; 49 cognitively normal controls	cross-sectional	PET, ROI	relationship between Aβ- and tau-based AD pathologies and NPS	not specified	bilateral frontal, anterior and posterior cingulate, lateral parietal and lateral temporal cortices and whole cerebellum; entorhinal cortex and hippocampus, medial temporal and limbic region, neocortical region, and uptake of inferior cerebellum	$p<.05$, Bonferroni multiple comparisons	no significant results

Notes. In the participants' column, the first sample size provided is the total number of participants with AD and/or MCI (inclusive of non-psychosis controls; if healthy controls are also included, these are reported at the end of the cell); where the symptom of interest was present in a smaller ratio of this, this is specified consequently (as numbers or percentages, as available in the study); assessment tools such as MMSE and CDR are only reported in the confounding factors where these were specifically included in the analyses, while complete neuropsychological assessment was not reported in this table; unless differently stated, the neuropsychiatric picture for the sample of interest was not available (e.g., unknown if the participants presenting with delusions also presented with other symptoms); findings of the studies are only reported in relation to the symptoms investigated (i.e. psychosis); all groups (sample with symptom of interest and control group) were used in the analyses which resulted in reported findings, unless differently stated; findings are only reported for the symptom of interest, therefore no significant findings only refers to that (i.e. the study might have other significant findings with respect to other NPS that are not reported here). *Abbreviations*. CMRgl=cerebral metabolic rate for glucose, FD=fractal dimension, DMN=default mode network, GCA-F=global cortical atrophy-frontal, LBD=Lewy body dementia, MTA=medial temporal lobe atrophy, NOS=not otherwise specified (dementia), PA=posterior atrophy, FDR=false discovery rate, FWE=family wise error, iRSFC= intuitive resting-state functional connectivity, SN=salience network

**These studies performed investigations on other neuropsychiatric symptoms/clusters of symptoms as well

***These studies included investigations on delusions, and/or hallucinations as individual symptoms

Two of these found bilateral hippocampal atrophy (Lee et al., 2019; Y.-M. Lee et al., 2021); the second one (Y.-M. Lee et al., 2021) also highlighted general temporal (also found in Misquitta et al. (2020)), and bilateral entorhinal and parahippocampal atrophy (with the last brain region also reported in McLachlan et al. (2018)), particularly in relation to the misidentification subtype). One study (Ramusino et al., 2021) identified right global cortical atrophy of the frontal lobe in association with psychosis, while another (Siafarikas et al., 2021) highlighted an association with the post-central gyrus of the lateral parietal lobe. Lower volume in the anterior cingulate, lateral frontal, lateral occipital, lateral parietal, and medial orbitofrontal was found by Rafii et al. (2014) in MCI and AD patients with psychotic symptoms compared to those without. At 1-year post-baseline, lower volume was found in the lateral frontal and lateral parietal cortex after controlling for baseline ADAS-cog performance. Lastly, another longitudinal study (Jeong et al., 2021) found that reduced cortical thickness in the right and left caudal anterior cingulate cortex was associated with a higher risk of incident psychosis after transition from amnestic MCI (a-MCI) to AD dementia, also when adjusted for hippocampal volume. Voxel-based morphometry was used in three studies, two on the general psychotic cluster, which found atrophy in the right anterior-inferior temporal lobe, extending to the fusiform gyrus (D'Antonio et al., 2019) and fronto-orbital cortex, anterior cingulate cortex, and the thalamus (Makovac et al., 2016), and one (Lee et al., 2016) which found lower volume in association with the misidentification subtype (misidentification delusions and/or hallucinations), mainly in the right middle frontal gyrus, middle temporal gyrus, inferior parietal lobule and the occipital lobe. Lastly, D'Antonio et al. (2021) performed a region-based morphometry analysis by extracting cortical complexity values and found reduced cortical complexity in the right ventromedial visual cortex in association with psychosis; in addition, they found the misidentification subtype associated with decreased cortical complexity in the right entorhinal cortex.

3.4.6.2. Hypo and hyper perfusion measured with SPECT

Four studies investigated hypoperfusion in association with psychosis, with different findings: Kotrla et al. (1995) identified hypoperfusion in the parietal lobe. Mega et al. (2000) highlighted associations with several regions: left medial orbital frontal, anterior cingulate, dorsolateral frontal and parietal, pulvinar, ventral striatum, cerebellum, right

dorsolateral and medial frontal. A study by Moran et al. (2008) identified gender differences: hypoperfusion in the right inferior-lateral prefrontal cortex and right mid-temporal cortex among female patients, while links to the right striatal cortex were found among male patients. Lastly, Banno et al. (2014) identified the right angular gyrus and the right occipital lobe in association with a psychotic cluster which included agitation.

3.4.6.3. Hypo and hyper metabolism measured with PET

The findings of the three studies which employed FDG-PET to analyse psychosis as a cluster highlight key areas of hypometabolism in the temporal cortex (Cappelletto et al., 2021; Lopez et al., 2001), and frontal cortex (Koppel et al., 2014; Sultzer et al., 1995); another using PET identified the dorsolateral cortex (Lopez et al., 2001).

3.4.6.4. Use of MRI to Study WMH

Misquitta et al. (2020) highlighted significant associations between psychotic symptoms and increased WMH load. Another study (Barber et al., 1999) focusing on AD and other types of dementia, conversely, found an association with the absence of occipital WMH and the presence of delusions and visual hallucinations.

3.4.6.5. Recent applications of fMRI

In one study (Serra et al., 2020) a psychosis factor was identified that included the symptoms of delusions, hallucinations and disinhibition. By using fMRI, the authors noted regions of reduced connectivity in relation to this cluster that included frontal areas, the right cingulum, hippocampus, and insula, and bilateral supramarginal gyrus.

3.4.7. Meta-Analysis on delusions

As part of the aims, the possibility of performing a coordinate-based meta-analysis (CBMA) (Turkeltaub et al., 2002; Wager et al., 2003) was explored, aiming to localise the brain regions that were consistently associated with the presence of delusions, hallucinations, and psychosis. CBMA is a common approach to estimate how frequently the same brain areas or networks are found across independent studies that share comparable hypotheses (Tench et al., 2020), and which makes use of the statistical peak location(s) within clusters that are reported by the studies as x,y,z coordinates (Müller et

al., 2018); these are referred to as peak coordinates (Wager et al., 2007), and have been commonly reported either in the Talairach and Tournoux atlas, (Talairach et al., 1990) or in Montreal Neurological Institute (MNI) space (Evans et al., 1993). Therefore, for each study included in the systematic analysis, the peak coordinates of the significant clusters that were identified were extracted when these were made available in the study. The studies were divided according to the symptoms of interest, finding that data was available in a suitable number of studies (n=14) only in those that focused on delusions. Only n=1 and n=5 studies reported suitable data in the hallucination and psychotic cluster studies, respectively, and these small numbers of studies were not deemed suitable for performing meta-analyses. Only the studies which provided information on significant peaks in association with the symptom of delusions (n=14) (Table 3.2) were included in the meta-analysis, with no restrictions in terms of neuroimaging technique employed, analytic method, sample size (excepting case studies), and number of reported peak clusters. Two studies performed analyses on the severity of delusions in association with brain atrophy (Fischer et al., 2016; Nomura et al., 2012) (no control sample), while the remaining twelve compared AD patients with delusions to AD patients without delusions (Fukuhara et al., 2001; Nakaaki et al., 2013b; Nakano et al., 2005; Nakatsuka et al., 2013; Qian et al., 2019b; Qian et al., 2019a; Serra et al., 2010; Staff et al., 1999; Sultzer et al., 2014; Ting et al., 2015) and/or healthy controls (Boublay et al., 2020; Matsuoka et al., 2010); the total sample size ranged from eighteen to ninety-three, and the number of significant peaks for coordinates ranged from one to twenty-three.

Among the different CBMA meta-analysis methods, it was decided to perform a multi-level kernel density analysis (MKDA) (Kober et al., 2008; Kober & Wager, 2010), as this was deemed the most appropriate for the features of the studies included in the analysis. Compared to other common methods such as kernel density analysis (KDA) (Wager et al., 2003) and activation likelihood estimate (ALE) (Turkeltaub et al., 2002), the MKDA has the advantage of considering each set of peaks at the study level, rather than by only considering each independent peak as the unit of analysis (Kober & Wager, 2010; Wager et al., 2007). In this way, it accounts for differences in the number of clusters reported by each study (it accounts for the multilevel characteristics of the data), thus preventing studies with a higher number of coordinates from weighting

disproportionately in the meta-analysis (Salimi-Khorshidi et al., 2009): for this reason it is advised when the studies present with a heterogeneous number of clusters, such as those found in this case. Information concerning the peak coordinates and sample sizes of the fourteen studies were analysed using an MKDA algorithm, made available on NiMARE (Salo, 2022), a Python package developed to perform meta-analyses on coordinate-based neuroimaging data. As the algorithm requires MNI coordinates, the coordinates that were reported in the Talairach and Tournoux atlas space in the studies were transformed, using the validated converter tool included in GingerALE (Laird et al., 2010; Lancaster et al., 2007). The algorithm was run on Spyder (Version 5.3.3) (Raybaut, 2022), and False Discovery Rate correction (FDR) was applied (Salo, 2022), with a threshold of $z >= 1.64$ (equivalent to $p<.05$). This produced three clusters, that are reported in Table 3.5 and visualised in Figure 3.3. The uncorrected clusters (thresholded at $z >= 1.64$, equivalent to $p<.05$) can be found in the Appendix B. Lastly, the brain locations of the peak coordinates (Table 3.5) were estimated using the mni2atlas function (Mascali, 2022) in MATLAB (Version R2022b), which translates coordinates into labels from different atlases, and the MNI structural atlas (Collins et al., 1995; Mazziotta et al., 2001) was selected among these. Use of this atlas identified the following brain regions that were in closest proximity to the three peaks; all were in the right hemisphere: a cluster in the frontal lobe, one in the putamen and one smaller cluster in the insula.

Table 3.5

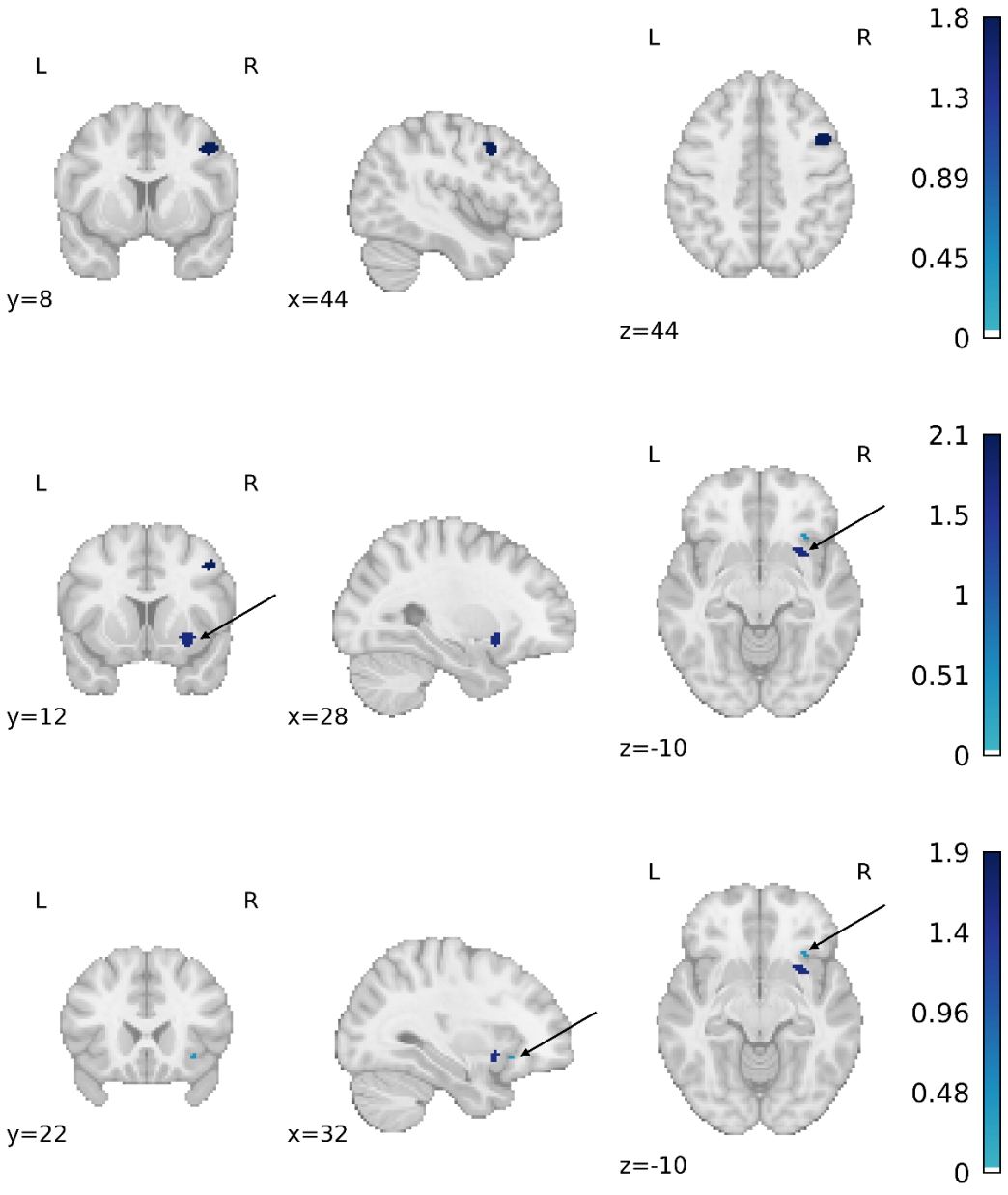
Peak clusters of coordinates derived from the meta-analysis on fourteen studies on delusions

Cluster ID	X	Y	Z	Peak Statistic (*z*)	Cluster Size (mm^3)	Label (MNI structural atlas)
1	44.0	8.0	44.0	1.859	608	R Frontal Lobe (74%)
2	28.0	12.0	-10.0	1.859	408	R Putamen (27%)
3	32.0	22.0	-10.0	1.859	40	R Insula (60%)

Notes. Coordinates are expressed in MNI space. FDR correction was applied; clusters are significant at $z >= 1.64$ (equivalent to $p<.05$).

Figure 3.3

Meta-analysis results



Notes. With reference to the MNI structural atlas, the coordinates correspond respectively to the R Frontal Lobe, the R Putamen, and the R Insula.

3.5. Discussion

To the author's knowledge, this is the first systematic review which synthesises the findings of all studies published up to the recent past (to 30th December 2021) that investigate the neuroanatomical correlates of psychotic symptoms in AD dementia and MCI, while also capturing and comparing the different neuroimaging approaches and methodologies.

The results derived from this systematic review and meta-analysis have highlighted a number of key brain areas and networks that appear to be linked to the occurrence and severity of psychotic manifestations in Alzheimer's disease, when these are considered together as a cluster, as well as separately in the form of delusions and hallucinations. Confirming the findings derived from previous reviews (Ballard et al., 2020; Gallagher et al., 2017; Ismail et al., 2012; Murray et al., 2014; Reeves et al., 2012), common areas of atrophy and change (e.g., in metabolism) were again identified predominantly in the frontal lobe, tending towards a right asymmetry. As expected, though, a greater number of regions was identified, which spanned all four lobes, most likely due to comprehensive capture of the wide variety of studies that report on various psychotic phenomena, and to factors intrinsic to the methodology of the studies, such as the severity of the samples included and neuroimaging technique that was adopted. The combination of findings has allowed consideration of potential underlying mechanisms, which other factors may contribute to the results, as well as highlighting directions for future studies in this area.

3.5.1. Observations derived from the systematic review and meta-analysis on delusions and delusional subtypes

As delusions were the most commonly studied symptom within the symptomology of interest, unsurprisingly a substantial number of brain regions were identified across the numerous studies. The synthesis of these studies provided here confirmed the findings of earlier previous reviews on delusions (Ismail et al., 2012; Reeves et al., 2012) in that some common areas could be identified, which may help explain the origin of delusional formation from a neuroanatomical point of view. Variation across studies was also noted that seemed to reflect the delusional subtype that was most prevalent within a

particular study, the neuroimaging approach that was adopted, in addition to the size and stratification of the sample along the AD continuum.

Summing up the brain regions that were identified, across the majority of the studies there was predominant involvement of frontal regions; this was evidenced both from the findings of the systematic review and the results of the meta-analysis (in which the right frontal lobe contained the largest cluster, as seen in the results using FDR correction (Table 3.5, Figure 3.3), and extensive frontal associations were detected when the uncorrected statistical threshold was applied (Appendix B)). The insula and the putamen appeared also to be of importance both from an analysis of the systematic review and the output of the meta-analysis. On the other hand, areas which were frequently identified by analysing the results of the systematic review, but not from the meta-analysis were temporal regions, as well as the anterior and posterior cingulate cortex. Concerning laterality, while the meta-analysis identified all three regions in the right hemisphere, in the systematic review there was also a predominance of right hemisphere brain regions, but this was not unequivocal.

Considering the links between delusions and the fronto-temporal regions, these areas are generally responsible for regulation of executive function and working memory, and for storage and retrieval of biographic memory, respectively (Uysal, 2023). This might suggest that greater atrophy in these areas could be associated with an inability to correctly remember and process information about self and others, which contributes to the formation of delusional beliefs. More specifically, the areas which were more frequently identified across the studies within the frontal lobe were the prefrontal cortex (mainly on measures of hypo-activation), and within this, the orbitofrontal cortex. These have been linked to the regulation of intentional and motivated behaviours (Rafii et al., 2014), memory and learning processes (Rolls, 2004; Stanislav et al., 2013), and assigning values to specific emotional inputs (Dixon et al., 2017). Among temporal areas, on the other hand, the most frequently identified were the parahippocampal gyri, responsible for memory encoding and retrieval (Yoo et al., 2012), context appraisal and associative learning (Aminoff et al., 2013; Prasad, 2019). The combination of these processes might help explain how the failure to assimilate the correct information and to consider alternative possibilities could generate and maintain the delusional belief (Sultzer et al., 2014).

Albeit with less frequency, areas associated with delusions were also identified within the parietal lobe, mainly the precuneus, which is involved in self-centred mental imagery strategies, episodic memory retrieval (Cavanna & Trimble, 2006), and discriminating self-relevant from self-irrelevant information (Nomura et al., 2012). With regard to the occipital lobe, this brain region was mainly identified within studies with participants that had a greater prevalence of misidentification phenomena (discussed below).

One limbic structure that was identified by a large number of the studies on delusions was the cingulate cortex, anterior and posterior. The anterior cingulate cortex is commonly subdivided into a dorsal and ventral portion; the dorsal anterior cingulate cortex is related to high-level cognition, such as executive functioning and error detection, as well as the processing of visual stimuli, while the ventral anterior cingulate cortex is mainly involved with emotional processing, such as regulation of overall affect, and assigning emotion to internal and external stimuli, and pain perception (Boublay et al., 2020; Jeong et al., 2021; Rolls, 2019): one interpretation might be that the impaired monitoring of reality functions, associated with abnormal perceptual and emotional experiences, might contribute to the development of delusions. Dysfunction of this region has been suggested in relation to most neuropsychiatric symptoms (Chen et al., 2021), as seen in Table 1.1 of chapter 1: this points towards the criticality of this brain region, that when affected by neuropathology, can contribute to concomitant symptom presentation, particularly at later stages of the disease, as seen in chapter 2. Furthermore, given the known link between anterior cingulate cortex and executive function (Mattavelli et al., 2022), and the key role that executive function seems to play in the manifestation of most psychiatric, including psychotic symptoms in AD, as seen in Table 1.1 (Chen et al., 2021), further investigation might be warranted into the nature of this association (e.g., one previous study in Parkinson's disease dementia patients Lewis et al. (2012) has suggested that the loss of neuronal integrity within this brain area plays an important role in the pathophysiology underlying executive functioning and psychotic symptoms). The posterior cingulate cortex, on the other hand, is mainly related to memory and visual processes, self-reflection and imagery (Rolls, 2019), and this was mostly identified in studies on delusions of misidentification, including Capgras syndrome.

It might be possible to explain further key processes through the involvement of the subcortical structures that were most frequently identified, such as parts of the basal ganglia (particularly the putamen). These brain regions are involved in the facilitation of different types of learning, particularly emotional (Luo et al., 2019), which might explain their involvement in the perpetuation of delusions.

Furthermore, both the meta-analysis and the systematic review identified the insula, which is involved in the perception of self-generated stimuli, the awareness of external stimuli, and maintaining rigidly held beliefs (Ting et al., 2015). The insula and the anterior cingulate cortex are part of the salience network (Uddin, 2017). Their involvement might therefore explain the difficulty that patients with delusions have in discriminating, processing, and filtering relevant stimuli. The salience network has been highlighted in previous models on delusional formation, such as the 'aberrant salience' hypothesis (Kapur, 2003): this refers to the attribution of motivational salience to irrelevant stimuli, generating distorted interpretations, and it appears to be linked to dysfunction in dopamine regulation, which might lead to the unfounded associations that are characteristic of delusional beliefs, as it causes irrelevant stimuli to receive excessive salience. Support for this model has been provided by functional neuroimaging studies on delusions in other psychiatric disorders (Panula et al., 2022; Roiser et al., 2012), as well within a review on the origins of delusions in AD (Reeves et al., 2012), which seems to indicate disruption of this network across different syndromes, and its contribution to the generation mechanism of delusional beliefs. Furthermore, there similarly appears to be some evidence that dysfunction within this network precedes delusional formation in both AD patients (Jeong et al., 2021) and other psychiatric disorders (Raij et al., 2016), again pointing toward its importance as a target for further investigation.

Concerning laterality, as expected, the majority of areas of atrophy and hypoperfusion/hypometabolism were identified in the right hemisphere (Ismail et al., 2012), albeit not exclusively. Potentially of equal interest, areas of hyperactivation were on the other hand identified within the left hemisphere. It has been hypothesised in different models of delusional formation (Devinsky, 2009; Gurin & Blum, 2017), that this might be linked to the fact that while less activity in the right hemisphere might be linked to deficits in the interpretation of external and internal data, as well as social cues, regions in the left hemisphere could be involved in creating alternative explanations.

With respect to the thematic aspects of delusional content, contrary to expectations, clear trends were not identified with respect to each individual delusional subtypes; this is likely due to the fact that, to date, this approach has been taken by so few studies, and these were methodologically different. Thus, it appears preliminary to draw conclusions, and further investigations of delusional subtypes are likely to be worthwhile. However, some correspondence between studies appeared clearer when considering delusions that relate to paranoid aspects (such as theft, persecution, abandonment) versus those that relate to misidentification phenomena such as Capgras syndrome (with this investigated in a few studies, particularly case-studies), which might suggest a neuroanatomical justification for this phenomenology based classification proposed in chapter 1 and the notion that different manifestations are underscored by different key mechanisms. Specifically, fronto-temporal involvement was particularly evident in association with paranoia, while regions across the four lobes and a greater involvement of the cingulate cortex (particularly the posterior portion, as mentioned above) were identified in association with misidentification. Therefore, the evidence seems to suggest that a more fine-grained classification of the delusional subtype might constitute an interesting approach to undertake (see below).

3.5.2. Observations on hallucinations

Although fewer studies focused on the neuroimaging correlates of hallucinations, some interpretation of the findings is possible. While associations were identified with multiple regions across the brain, the occipital lobe was consistently mentioned in most studies in relation to visual hallucinations, (but not in the single study that investigated musical hallucinations), suggesting a modality specific neuroanatomical impairment that underpins specific types of hallucinations. An association with the anterior cingulate cortex was frequently identified, and in one key study (Blanc et al., 2014), the insula, suggesting a disruption of the salience network in the formation of hallucinations, as well as delusions, and offering a potential explanation for why these symptoms can tend to co-occur.

Furthermore, involvement of frontal brain regions was identified in two studies (Blanc et al., 2014; Boublay et al., 2020); a combined impairment of frontal and occipital areas may indicate diminished sensory processing of visual stimuli (Zhang et al., 2023) and

deficits in predictive coding, the ability to correctly implement generative models in the brain to interpret sensory inputs (Kocagoncu et al., 2021). Previous studies have suggested an association between non-optimal predictive processing and the presence of hallucinations (Horga et al., 2014; Sterzer et al., 2018), underpinned by prediction errors. Combined, these processes might explain the misinterpretation of stimuli and misperceptions which underlie visual hallucinations; further investigations into these processes might be warranted to increase the understanding of hallucinations in AD.

There were also a number of studies that did not identify any brain regions in association with hallucinations, although this was mainly found in those that investigated the associations of all neuropsychiatric symptoms, with the potential consequence that the participant samples did not exhibit hallucinations to a sufficient prevalence, and were therefore not optimal for the study of this symptom. More studies are needed that focus specifically on the neuroanatomical underpinnings of hallucinations at different stages of the AD continuum, so that variability in the incidence of hallucinations may be accounted for (as hallucinations tend to be less common at earlier stages of the disease (Linszen et al., 2018)).

3.5.3. Psychotic clustering and an alternative approach to classification: misidentification and paranoia

Considered that the studies that investigated psychosis as a cluster were predominantly inclusive of symptoms of delusions and/or hallucinations, as might be expected, they showed a vast degree of overlap with areas identified above when approaching the symptoms separately: reporting involvement mainly of frontal, temporal and occipital areas, as well as the anterior cingulate cortex.

Analysing the key findings of the studies that specified the content of psychotic symptoms, a pattern emerged that seems to confirm that the two distinct phenotypes of misidentification and paranoia, introduced in chapter 1, can be identified (D'Antonio et al., 2019; Ismail et al., 2012). The neuroanatomical correspondences of these two manifestations could support the identification of new criteria to reflect this (Cook et al., 2003; Perez-Madriñan et al., 2004), recently revisited in an international effort to update the criteria for psychosis (Fischer, 2020).

According to this proposed means of classification (Cook et al., 2003), in order to identify the brain areas in relation to misidentification, all the studies which included in their sample participants presenting delusions of misidentification, such as Capgras syndrome and phantom boarder were considered, as well as their similarities with the findings of the studies on hallucinations; within the paranoia subtype, delusions of persecution, theft, abandonment, and jealousy were considered.

This revealed that the misidentification subtype was the most frequently studied, and it was quite consistently found in association with a more severe overall clinical picture compared to the paranoid one (Lee et al., 2016). The misidentification subtype frequently showed associations with frontal, occipital and temporal lobe regions, while within the paranoid subtype, associations with temporal lobe regions were found much more often, with a smaller contribution of frontal areas.

Specifically, within the misidentification subtype, the posterior cingulate, prefrontal and orbitofrontal cortices were frequently identified, as well as the lingual gyrus of the occipital lobe, and impairments in the ventral visual stream: this might suggest that misidentification phenomena in AD are, at least partially, related to misperception and misinterpretation of stimuli (D'Antonio et al., 2019).

Concerning the involvement of temporal areas, while these were found in both subtypes, two recent studies identified the entorhinal cortex in relation to misidentification; the entorhinal cortex is involved in the perceptual processing of stimuli, in novelty detection, associative learning, and processing episodic, recognition, and autobiographical memory, which might contribute to explaining its involvement within phenomena of misidentification (Prasad et al., 2004). Importantly, this appears to be the case also when statistically controlling for disease severity, as both studies included measures of cognitive impairment as covariates in their analyses. Therefore, while both the entorhinal cortex (Braak et al., 1993) and misidentification phenomena are associated with a more severe clinical picture, their association appears to be found irrespective of this, suggesting an interesting route to further investigate in the future.

With regard to the delusional subtypes that had an underlying paranoid component, the most commonly identified regions were fronto-temporal areas and the anterior cingulate cortex, which might indicate a shared mechanism explaining this category of

delusional content. Atrophy in the temporal cortex in relation to different aspects of paranoia might be linked to a misinterpretation of stimuli and failure to accurately encode new memories, as well as an increased sensitivity to perceive emotional pain and emotions that have a negative connotation (Nakatsuka et al., 2013). However, very few studies focused on particular types of paranoid delusions (e.g., theft, jealousy, abandonment) and attempted an interpretation of different mechanisms underpinning each thematic component; not enough to enable the differences and similarities of associated brain regions to be assessed more clearly.

Comparisons between studies such as those mentioned above that link neuroanatomy to each type of delusional phenomena may be informative in shedding light on why one category of delusions may occur over another, as well as informing on the potential shared mechanisms between certain subtypes of delusions and hallucinations. Nevertheless, it remains that the summaries of brain regions that are linked to each subtype need to be interpreted with caution, as substantial methodological differences were present across the studies that treated the symptoms separately, and further investigations in this area will help to clarify these mechanisms.

3.5.4. Other neuropsychiatric symptoms within the psychotic cluster

When approaching psychosis as a cluster, studies normally included participants who presented with delusions and/or hallucinations, while on three occasions another symptom was included in the cluster.

In one study this symptom was disinhibition, which in a preliminary analysis was factored within the same cluster (Serra et al., 2020): it was hypothesised that the role of large subnetwork found, comprising the hippocampus, frontal areas, cingulum, insula, and supramarginal gyrus, is linked to regulating higher-order behaviours, which might explain its association with a psychotic cluster inclusive of disinhibition as well.

On the other hand, the two studies in which sleep disorders were clustered within psychosis did not yield any significant results in relation to associations with neuroanatomy. While it appears that sleep dysfunction and psychosis are related phenomena, and many theoretical models have been proposed to explain their relationship (Reeve et al., 2015), clear mechanisms in relation to brain regions or

networks, particularly within the context of AD, are yet to be understood. Therefore, should this clustering be seen regularly, exploring the reasons for it, whether neuroanatomical or due to other factors, might be something worth doing in future investigations.

3.5.5. Observations on the methodological differences among the studies and considerations from the risk of bias assessment

A range of data was extracted in this review with the objective of attempting to explain potential sources of variance that may affect the findings for the neuroanatomical regions that link to psychosis in AD. Analysing the methodological differences among the studies, some of the features that were considered to be of potential importance seemed to contribute to this. One such aspect was in relation to sample size and composition. While unexpectedly the results of studies with very large sample sizes for example Moran et al. (2008), were found to be mostly comparable to the majority of the studies that had smaller numbers of participants, when interpreting the studies that did not find any significant results, on many occasions this seemed to be related to the small percentage of participants presenting with the symptoms of interest within the overall sample. Future studies should ensure that the sample size is sufficient for those with the symptom(s) of interest to be adequately represented.

Furthermore, variability was found in relation to the choice of a control sample: while some studies did not employ one, focusing on aspects such as the correlation of neuroanatomical regions with the severity of symptoms, the majority of studies performed group comparisons, either with an AD sample that did not exhibit psychotic symptoms, or cognitively healthy controls. While the approach to matching the controls was normally identified, mainly through similarities in terms of age, level of education and severity of the cognitive impairment, this was not always the case; furthermore, control for the presence of other neuropsychiatric symptoms was normally not performed, which might be a factor to consider in future studies, in order to identify regions that are more certainly specifically linked to psychotic symptomology. If group comparisons are used to isolate neuroanatomy specific to the symptoms of interest, it is suggested that an appropriate control group is one matched to the group of interest, on factors such as sample size, disease stage age, gender, and other neuropsychiatric

symptoms. Often it is desirable for the control group to differ from the other group on the symptom of interest only, but of course in practice this is unachievable. In the case of correlation/multiple regression, similar factors, for example, age, gender, disease stage, and other neuropsychiatric symptoms, might be considered as covariates. In both types of statistical modelling, analyses should be performed and reported, with and without certain covariates, such as indicators of disease severity (which may take the form of cognitive or neuroanatomical markers), so that the differences between the results may be assessed, as these may be informative when attempting to understand the brain regions and networks that link to the psychotic symptom of interest.

One element that was particularly evident from the results of the risk of bias assessment analysis, was the variability in terms of what covariates were included in the analyses, or more generally, what potentially impactful aspects were considered. One important example of this was the lack of consideration of disease stage, which appeared to be linked to non-significant findings in some studies, indicating that this might be an important aspect to consider in future analyses. Taking into account how the prevalence may change as the disease progresses (Ballard et al., 2020; Ismail et al., 2022), as seen in chapter 2, it appears clear that careful consideration of disease stage in sample selection is likely to be important. With regard to neuroimaging methodological aspects, a minority of studies did not specifically state whether they controlled for factors such as total intracranial volume for MRI and mean metabolic rate for PET. However, no clear and consistent differences were identified between studies that did adopt these procedures compared to those that did not, which was contrary to what expected. However, as further investigation on the methodology was not pursued beyond what was reported in the studies, it is possible that even when not clearly stated, strategies to account for these factors were taken into account (and it is reporting standards that has been the issue rather than inclusion of covariates).

Studies which employed ROI and VB approaches to analyse structural and functional data, overall provided comparable findings. However, in the cases where the pre-selected brain areas in ROI studies were limited to one or two specific regions, which did not result in significant associations, they might have overlooked the importance of other relevant regions, appearing to suggest that focused ROI analyses should also be

accompanied by whole-brain voxel (or vertex)-wise analyses (and these other analyses could be very useful for future meta-analyses).

Furthermore, other discrepancies across studies may potentially relate to the procedural and statistical approaches taken (including, for example, the means of correction for multiple comparisons), as well as the type of information (reporting standards) which was made available within the studies to allow for clear synthesis and comparisons.

In confirmation of recent evidence on the prevalence of psychotic manifestations at earlier stages of AD pathology (Fischer, 2020; Ismail et al., 2022), studies that included MCI in their sample tended to find comparable results to those who did not, with involvement of frontal and orbitofrontal areas, anterior cingulate cortex and insula appearing to be evident in associations with these symptoms at this earlier stage (Fischer et al., 2016; Jeong et al., 2021; Koppel et al., 2014; Misquitta et al., 2020; Rafii et al., 2014; Ramusino et al., 2021; Serra et al., 2020). However, these were typically investigated within a larger sample comprised of both MCI and AD participants, therefore, to further clarify this, investigations focusing only on preclinical or prodromal stages, where symptoms might be more likely to be observed in isolation, could constitute a useful future approach. Similarly, studies that had a longitudinal design tended to consistently identify similar areas as those with a cross-sectional design.

Although the most common tool used by some margin was the Neuropsychiatric Inventory (Cummings et al., 1994), studies that employed different standardised questionnaires or interviews, those that based their diagnosis on the set of criteria, and those that approached it with unstandardised methods (e.g. clinical observation or interviews) did not have any clear and consistent comparable differences on their overall results.

At the same time, though, clarity over the classifications of psychotic symptoms is a key area to address in future studies: few studies have focused their analyses on specific psychotic symptoms that can be detected by the tools in order to pinpoint the precise areas related to that particular type of manifestation, and this might be an interesting approach to consider in the future (in order to consider the unique associations that might be observed between certain symptoms and brain regions, as well to understand

the commonalities that can be found across delusional subtypes). Similarly, more accurate depiction of the frequency and severity of the symptoms within the sample of participants with psychotic symptoms, which was not always adequately captured or described within the papers studied, might also help to clarify their neuroanatomical underpinnings, with respect to their course within the AD continuum.

3.5.6. Limitations

Some methodological limitations to this review should be considered. First of all, in relation to the included studies, the authors were not contacted to enquire about potential missing data or aspects of their methods that may have been missing from the published reports: this is likely to have had an impact both on the tables of results produced by the systematic review (whereby some cells which currently state “not specified” might have been otherwise filled), and importantly, on the opportunity to perform a meta-analysis inclusive of all the studies. As it was, only the peak coordinates that were readily available from the studies were considered which meant that it was only possible to perform a meta-analysis on a subset of studies that focused on delusions only and it was not possible to proceed with one on hallucinations or on the psychotic cluster. Other limitations of the meta-analysis should also be taken into account, mainly the fact that the subset of studies, while homogeneous in terms of focusing on delusions, were heterogeneous with respect to other aspects, such as the neuroimaging techniques employed and the stratification (disease staging) of the samples. As the literature develops in these areas, further opportunities for meta-analyses should be explored, and analysis of raw data or, for example, contrast images, would minimise any bias relating to using the cluster peaks only.

One limitation related to the methods, in that only publications that were available in English were considered, which led to an a-priori exclusion of five papers which were published in other languages.

Furthermore, while the quality of the studies was assessed using a validated tool, this only revealed the overall quality with respect to certain aspects and as a consequence certain key features may not have been captured. This meant that when presenting the results of the tool, studies that may appear similar in quality may actually have had different methodological strengths and weaknesses in terms of sample sizes and

accuracy in control matching, as well as different approaches to the analytic and statistical methods, and level of details provided on the significance threshold and correction methods employed. The lack of consideration of some of these other factors through using the chosen instrument might mean that certain studies have been classified as being of high quality, using the available criteria, while they have some quite significant shortcomings. Future systematic reviews in this area should consider these other factors (e.g., by customising or creating a new quality control or weight of evidence tool so that it is able to capture these additional methodological features).

Lastly, with respect to the psychotic symptom cluster category, some studies were specific in terms of sample composition (e.g., within the sample, how many participants presented with only delusions, how many presented with only hallucinations, and how many presented with both types of symptoms), while in others this was not clearly specified. This might constitute a limitation of the grouping chosen for this category, as the prevalence in the symptoms manifested might therefore be variable across the studies. Similarly, within the studies that focused either on delusions or hallucinations only, it was not always specified whether people with the other symptom were excluded (or included) the sample with few exceptions (there was one, for example, in which the presence of other neuropsychiatric symptoms was included as a covariate in the analysis). Going forward, authors should report the full characteristics of their samples to assist future synthesis and comparisons between studies, and investigators might also consider study designs where samples are recruited on the basis of one key symptom and who are excluded on the basis of another, or by accounting for other types of symptoms as covariates in the analyses.

3.6. Conclusions and future directions

The aim of the systematic review exposed in this chapter was to systematically analyse and synthesise the findings of the neuroimaging studies that have investigated the brain regions and networks linked with psychosis in AD, in an effort to clarify the neuroanatomical underpinnings of these symptoms. To the author's knowledge this is the first comprehensive review, performed with a specific focus on neuroimaging and psychotic symptoms, that has used a detailed protocol for article discovery and data extraction. It was also attempted to include all studies on these topics from when

neuroimaging was first adopted to only the recent past (Dec 2021) and has been inclusive of a range of different imaging modalities (e.g., MRI, PET, SPECT). Analysing the findings both from a holistic perspective, and an individual focus through thematic grouping of studies has allowed for a synthesis of the main neuroanatomical correlates of psychosis as a cluster of manifestations, as well as with respect to individual symptom types (e.g., delusions vs. hallucinations) and subtypes (e.g., misidentification vs paranoia). While some brain regions/networks could be identified that relate to psychotic manifestations as viewed broadly, for example the key role of the anterior cingulate cortex, clearer distinctions appeared evident when considering thematic differences, with regions localised in fronto-temporal areas in the case of delusions, and fronto-occipital areas in relation to hallucinations. Further distinctions could also be made between misidentification phenomena, that were mainly related to fronto-occipital areas, and paranoid delusions, that were mostly associated with temporal areas. While this line of research is not without its challenges, being able to study the correlates of distinct symptom types has the advantage of offering a more precise understanding of the different clinical profiles. The key findings of this review provide clarification on this topic, and provide support to the most recent directions that have been undertaken with respect to the need for new criteria for the classification of psychosis in AD as seen in chapter 1 (Fischer, 2020), and they include: 1) the identification of neuroanatomical associations with regard to psychotic symptoms, and particularly when considered with regard to their content-related differences; 2) information on the associations that can be found with specific brain regions in those at earlier stages of disease, however it is highlighted that there is a need for further investigations of this kind, in an effort to clarify neuroanatomical underpinnings when symptoms may be most discrete; 3) there is a need for the inclusion of important covariates within the analyses, such as disease severity (which could be, for example, via clinical scales or biomarkers), as well as the necessity for clear and accurate reporting of analytic approaches in scientific articles; and 4) there is a need for carefully considered and thorough measurement of psychotic phenomenology in future studies, to ensure that unique and shared associations with brain regions and networks can be identified.

Chapter 4 – Study 2: The role of regional atrophy in the manifestation of psychotic phenomena in Alzheimer's disease dementia and Mild Cognitive Impairment

4.1. Overview

In chapter 3, a systematic review and meta-analysis was performed, which highlighted that key brain regions, predominantly in the right frontal lobe, the anterior cingulate cortex, and temporo-occipital areas are associated with different manifestations of psychotic symptoms. Specifically, fronto-temporal areas were identified in relation to delusions, fronto-occipital areas were linked to hallucinations, while fronto-temporal and occipital areas, as well as the anterior cingulate cortex were linked to the psychotic cluster. The review highlighted great variability in terms of study design, particularly concerning the approach to the definition of psychosis as identified above, as well as neuroimaging techniques employed, which yielded variable results. In this chapter, these points are addressed, based on objective 3 of this thesis, by investigating the associations with different classes of psychotic symptoms in AD dementia and MCI due to AD and comparing the outcomes of three methodological approaches: Region of Interest (ROI), including brain areas identified in chapter 3, and whole-brain Voxel based morphometry (VBM) and Surface based morphometry (SBM). Samples were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Participants with psychotic symptoms and control samples were selected based on their scores on the Neuropsychiatric Inventory (NPI), classing participants into: a psychotic cluster group consisting of participants who presented with either delusions, hallucinations, or both; two sub-groups comprising of participants who presented with delusions only and hallucinations only; based on the themes of the psychotic phenomena, two sub-groups comprising of misidentification and paranoia, and within the paranoid delusions, a further sub-group formed by delusion of theft only (the most common subtype). Controls for this study were matched based on disease stage (AD or MCI due to AD), age, gender, education, overall NPI score, MMSE and MOCA score for their neuropsychological profile, and their APOE4 status. Using T1-weighted MRI scans, the difference in regional atrophy between the participants presenting with the symptom of interest and the controls was assessed through ROI, VBM and SBM. Within the ROI approach, using SPSS (version 28), a series of multiple regressions was performed, to investigate the associations between the symptoms of interest, and the brain areas

previously identified (consisting of measures of cortical and subcortical volumes, cortical thickness, and surface area, provided through ADNI as part of their analyses using the FreeSurfer software). Within the whole-brain approaches, the original MRI scans of the participants were used to perform voxel- and surface-based morphometry, using the software Statistical Parametric Mapping (SPM) and one of its toolboxes CAT12: t-tests were then performed to compare differences between all the sub-groups with the symptoms of interest and their matched controls. This chapter ends by discussing the findings and reflecting on the implications of this study: in confirmation of the hypotheses, variation in certain brain regions is associated with psychotic phenomena generally, while others appear to be related to specific themes, and overlap in the findings across the different techniques is only partially present, providing support for the notion of employing complementary approaches.

4.2. Introduction

As discussed in chapter 1, the study of psychotic symptoms has been approached in different ways depending on the perspective taken for how these symptoms are conceptualised and classified. Studies on the neuroanatomical and neurobiological correlates of each symptom (Fischer & Sweet, 2016), that attempt to shed light on whether there are different underlying mechanisms behind the two symptoms have typically focused on the study of delusions and hallucinations separately. Similarly, studies that have focused on clinical outcomes, as well studies that have considered symptom prevalence along the AD continuum (DeMichele-Sweet & Sweet, 2010; Hollingworth et al., 2012), suggest that these symptoms are better studied separately, (e.g., the presence of hallucinations more frequently associated with increased severity of disease and mortality (Christie et al., 2012), and delusions tend to manifest earlier compared to hallucination along the disease continuum (Scarmeas et al., 2005; Zhao et al., 2016)). On the other hand, studies which have highlighted the heritability and familial aggregation of psychosis in AD (Shah et al., 2017) support the notion that a psychotic cluster, which combines delusions and hallucinations, manifests within AD as a distinct phenotype (Sweet et al., 2003) with a heritability estimated at 61% (Ismail et al., 2022). This approach has been further supported by factor analysis investigations on the neuropsychiatric manifestations of AD (Aalten, Verhey, et al., 2007; Wadsworth et al., 2012) and MCI (Van der Mussele et al., 2013), as seen in chapter 2 of this thesis. Lastly,

as discussed in chapters 1 and 3, in more recent years a new approach has emerged (Cook et al., 2003; Fischer, 2020) suggesting that a further means of classification of psychotic phenomena should be to consider the thematic subtypes of misidentification and paranoia, in order to understand their underlying mechanisms.

The results of the systematic review in chapter 3 indicated that while some brain regions/networks could be identified that relate to psychotic manifestations as viewed broadly, clearer distinctions appeared evident when considering the individual symptoms and their thematic differences. In fact, while fronto-temporal and occipital areas, and the anterior cingulate cortex were found to be associated with psychosis considered as a cluster, fronto-temporal areas as well as the cingulate cortex, the insula and the putamen were most frequently identified in relation to delusions, and with respect to hallucinations, the occipital lobe was consistently mentioned in most studies, followed by frontal brain regions. When considering the thematic patterns of misidentification and paranoia, it was found that the misidentification subtype frequently showed associations with frontal, occipital and temporal lobe regions, while for the paranoid subtype, associations with temporal lobe regions were found much more often, with a smaller contribution of frontal areas. Lastly, in relation to all psychotic phenomenology, laterality was overall slightly tending towards the right hemisphere, albeit not exclusively. The systematic review highlighted that notable progress has been made in the past three decades in identifying brain areas and networks associated with the presence of delusions and hallucinations in AD dementia and MCI through the application of a range of different neuroimaging techniques. However, clarity is still required as different results emerged based on the different approaches to the definition of psychosis as identified above, as well as when different neuroimaging techniques were employed from the studies. While within the systematic review, all neuroimaging methods were considered, this study will focus on original analyses of magnetic resonance imaging (MRI) data that is available via ADNI. This datatype enables the study of grey matter atrophy, and focus may be placed upon specific brain regions using a Region of Interest (ROI) approach (typically using automated segmentation software such as FreeSurfer (*FreeSurfer*)), or by conducting whole brain analyses (voxel or vertex-wise) through Voxel-based morphometry (VBM) (Ashburner & Friston, 2009) or Surface-based morphometric (SBM) methods (Fischl et al., 1999). While VBM primarily estimates grey matter (GM) volume for cortical and subcortical areas, SBM is used to estimate

indices of cortical morphology, such as volume, thickness, area, and gyrification (Goto et al., 2022). Previous studies have used the ADNI database to perform analyses on the associations between neuroanatomical data and psychotic symptoms, however none of these focused on studying the differences between correlates of different themes (i.e., misidentification and paranoia) underlying this cluster of symptoms, rather considering delusions (Fischer et al., 2016; Ting et al., 2015) and hallucinations (Blanc et al., 2014; Donovan et al., 2014) as individual symptoms, or grouped together within a psychotic cluster (Koppel et al., 2014; Misquitta et al., 2020; Rafii et al., 2014). Furthermore, either a VBM (Fischer et al., 2016; Ting et al., 2015) or ROI approach (Donovan et al., 2014; Rafii et al., 2014) was previously adopted, thus comparisons were not drawn across the results of different approaches. Lastly, the majority of the studies was performed between 2014 and 2016, therefore the only data available was limited to the participants of the first protocol of the ADNI project, with only one exception (Misquitta et al., 2020), in which an MRI analysis was performed to investigate grey matter atrophy and white matter load associated with the psychotic cluster, without investigating the individual associations with each manifestation as this study aims to do.

Based on these considerations, the aim of the current study (study 2 of this thesis) is to investigate how regional atrophy using T1-weighted MRI scans and ROI data (made available from the data of protocols two and three of the ADNI database), related to the presence of different manifestations of psychotic symptomology within a sample of people diagnosed with AD, and MCI due to AD. This was done by considering 1) psychotic symptoms as a cluster, 2) delusions and hallucinations as individual symptoms, and 3) the thematic components of misidentification and paranoia, and within this, of delusions of theft only. Comparisons were made using three different analysis techniques: Region of Interest (ROI), and whole brain Voxel based morphometry (VBM) and Surface based morphometry (SBM).

4.3. Methods

4.3.1. Alzheimer’s Disease Neuroimaging Initiative (ADNI)

The data was obtained from ADNI (*ADNI | Alzheimer's Disease Neuroimaging Initiative*, 2026), which, as introduced in previous chapters 1 and 2, includes neuropsychiatric,

neuropsychological, and neuroanatomical data from participants, who are assessed yearly. Similarly to study 1 (chapter 2) the present study used data from ADNI 2 and 3 protocols. Specifically, the Neuropsychiatric Inventory (Cummings et al., 1994) data was used to select the samples of participants who presented with psychotic symptoms, MRI data to study the neuroanatomical differences in each subgroup, and demographic, neuropsychological and genetic data in order to match the control samples.

4.3.2. Participants

The participants included in this study (Table 4.1) were people who had AD dementia, or MCI due to AD, according to ADNI's inclusion criteria. Seventy participants were selected, who presented with either delusions, hallucinations, or both, based on their scores on the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), and had available neuroanatomical data from ADNI FreeSurfer data files. For the participants who presented with the symptoms at more than one visit, only the last one was selected. This was done so that only one visit per participant was included in the analyses; the latest time-point was selected in order to capture greater severity of the symptoms in some participants that might occur at earlier timepoints and thus provide more variance to enable a robust analysis. According to this, different groups of participants were selected: the psychotic cluster group was inclusive of the seventy participants who presented with either delusions, hallucinations, or both; a group was formed with participants who presented only with delusions, with thirty-nine participants, while nineteen participants formed the group of presenting with hallucinations only (twelve participants did not feature in either sub-group as they presented with both delusions and hallucinations). Two further groups were selected based on the thematic approach illustrated in chapter 1, with twenty-three participants presenting with hallucinations and/or the delusional subtypes relating to misidentification, and nineteen participants presenting with the delusional subtypes relating to paranoia, within which a final sub-group was created consisting of the participants who presented with delusions of theft only, which was the most common subtype, presented by sixteen participants (seventeen participants did not form part of any of these sub-groups as they presented with delusions relating to both themes, and eleven had positive scores only to the NPI delusions subtype called "other", therefore could not be identified within neither of the two groups). This process in depicted in the flowchart in Figure 4.1. Controls were

matched to each group with the same number of participants (pooling for each sub-group from the initial seventy controls matched to the group with psychosis) based on the following features: disease stage (AD or MCI due to AD), age, gender, education, overall NPI score, MMSE and MOCA score for their neuropsychological profile and genetic profile based on APOE4 (Table 4.1).

4.3.3. Neuropsychiatric Inventory

The NPI (Cummings et al., 1994) has been previously introduced in chapters 1 and 2, as a caregiver interview which evaluates and presence, frequency and severity of twelve neuropsychiatric features, including delusions and hallucinations, as well as collecting information on the subtypes of delusions and sensory modality of hallucinations. In this study, it was used to select presence (1) or absence (0) of: delusions (positive score on NPIA); hallucinations (positive score on NPIB); psychosis (positive score on NPIA and/or NPIB); misidentification (formed by the questions relating to hallucinations, NPIB1 to 7, in addition to the delusional subtypes of phantom boarders (NPIA4), Capgras syndrome (NPIA5), not recognising one's home (NPIA6) and television/magazine figures present in the house (NPIA8)); paranoia (formed by a positive answer to the delusional subtypes of fear of being in danger (NPIA1) theft (NPIA2), jealousy (NPIA3) and abandonment (NPIA7)); delusion of theft (NPIA2). The total numbers of people presenting with delusions and hallucinations subtypes from the NPI are reported in Table 4.2. For the analyses in this chapter, subgroups were formed based only on the reported presence of each symptom classification (disregarding the elements of frequency and severity).

4.3.4. Statistical analysis procedure

T1-weighted MRI scans were used to assess the difference in regional atrophy between the participants presenting with the symptom of interest and the controls. Two approaches were employed, one based on ROI, and one based on whole-brain measurements. Concerning the ROI approach, a series of logistic regressions was performed using SPSS (version 28) to investigate the associations between the symptoms of interest, and the series of brain areas previously identified in chapter 3, including regions in the fronto-temporal and occipital areas, the cingulate and entorhinal cortices, the insula, as well as sub-cortical areas such as the putamen (full list available in Appendix C). Brain area metrics available through ADNI are those derived

using the FreeSurfer software, and provided as measures of cortical and subcortical volumes, cortical thickness, and surface area (raw scores were used in the analyses: mm for cortical thickness, mm^2 for surface area and mm^3 for volumes). For each group, the likelihood of the symptom of interest presenting was assessed using the brain areas selected as independent variables in univariable logistic regression models. The estimated total intracranial volume available from the FreeSurfer dictionary (ST10CV) was used as covariate (Malone et al., 2015), to account for head size variability, in the analyses that tested the structural measures of volume and area (in the thickness models this was not done as unlike surface area and volume, cortical thickness is not correlated with TIV (Barnes et al., 2010; Schwarz et al., 2016)). No other covariate was included in the analyses as the controls were matched on age, education, gender, neuropsychological (using MMSE and MOCA), neuropsychiatric (using total NPI score) and genetic (using APOE4) profiles and disease stage (AD or MCI due to AD) as seen above. Lastly, Bonferroni correction based on the number of Regions of Interest (n = 42, multiplied by three for each metric used for a total of 126) and FDR correction were subsequently applied to account for multiple comparisons.

Within the whole-brain approach, the original T1-weighted MRI scans of the participants, made available on ADNI, were used to perform voxel- and surface-based morphometry, using the software SPM12 (Ashburner, 2014) and one of its toolboxes CAT12 (version 12.8.2) (Gaser, 2016), in MATLAB (version R2022b). The T1 MPRAGE (NifTI) images were segmented, spatially normalised to the MNI template and checked for homogeneity; in the voxel-based morphometry analyses, smoothing was set at 8mm, while in the surface-based morphometry at 12mm (Ashburner, 2014; Gaser, 2016). After preprocessing, t-tests were used to compare differences between psychosis subgroup and matched control samples, with age and total intracranial volume (computed from SPM) added as covariates in the VBM, while only age was added in the SBM analyses. Lastly, the brain locations of the peak coordinates were estimated using the atlas function provided within SPM12, which uses the MNI template (Evans et al., 1993) to generate labels. Results are reported at uncorrected p set at less than .001, with further exploratory analysis with uncorrected $p<.01$, with minimum cluster size was set at 25.

Table 4.1

Participants groups and demographic features

Symptoms group	Sample Size	Composition	Age, *M(SD)*	Gender	Education, *M(SD)*	MMSE, *M(SD)*	MOCA, *M(SD)*	NPI score, *M(SD)*	Disease stage	APOE4
Psychotic cluster	70	Positive score on NPIA and/or NPIB	72.80 (7.54)	34 Male 36 Female	15.87 (2.57)	22.08 (5.54)	14.85 (8.04)	22.34 (15.65)	16 MCI 54 AD	22 none 35 one copy 13 two copies
Control sample for psychotic cluster	70	Negative score on NPIA and NPIB	72.38 (7.36)	43 Male 27 Female	15.35 (2.65)	23.22 (4.77)	17.25 (6.90)	21.05 (8.45)	26 MCI 44 AD	27 none 31 one copy 12 two copies
Delusions	39	Positive score on NPIA	74.42 (7.22)	20 Male 19 Female	16.25 (2.70)	21.79 (5.29)	15.17 (7.40)	20.33 (12.94)	8 MCI 31 AD	10 none 20 one copy 9 two copies
Control sample for delusions	39	Negative score on NPIA and NPIB	73.41 (7.15)	21 Male 18 Female	15.30 (2.85)	22.07 (4.22)	15.74 (6.16)	20.42 (8.83)	9 MCI 30 AD	18 none 15 one copy 6 two copies
Hallucinations	19	Positive score on NPIB	71.98 (8.16)	9 Male 10 Female	15.47 (2.23)	24.68 (2.82)	17.26 (7.12)	19.05 (15.24)	6 MCI 13 AD	7 none 9 one copy 3 two copies
Control sample for hallucinations	19	Negative score on NPIA and NPIB	72.88 (5.42)	10 Male 9 Female	14.94 (2.94)	23.68 (3.00)	18.31 (4.58)	19.10 (9.66)	4 MCI 15 AD	8 none 9 one copy 2 two copies
Misidentification	23	Positive scores on NPIA4,5,6,8 and/or NPIB	73.29 (8.00)	10 Male 13 Female	15.26 (1.96)	24.30 (3.56)	16.69 (7.28)	19.26 (15.87)	7 MCI 16 AD	8 none 9 one copy 2 two copies

Symptoms group	Sample Size	Composition	Age, *M(SD)*	Gender	Education, *M(SD)*	MMSE, *M(SD)*	MOCA, *M(SD)*	NPI score, *M(SD)*	Disease stage	APOE4
Control sample for misidentification	23	Negative score on NPIA and NPIB	74.33 (7.72)	12 Male 11 Female	14.95 (2.71)	22.43 (4.70)	16.78 (6.35)	17.99 (6.09)	4 MCI 19 AD	8 none 9 one copy 2 two copies
Paranoia	19	Positive scores on NPIA1,2,3,7	73.29 (7.16)	12 Male 7 Female	16.10 (2.80)	22.31 (4.29)	15.36 (6.97)	21.21 (12.06)	5 MCI 14 AD	7 none 8 one copy 4 two copies
Control sample for paranoia	19	Negative score on NPIA and NPIB	72.91 (7.44)	9 Male 10 Female	15.10 (2.31)	21.47 (4.68)	14.57 (6.15	20.26 (7.14)	2 MCI 17 AD	11 none 6 one copy 2 two copies
Delusion of theft	16	Positive score on NPIA2	72.72 (7.23)	10 Male 6 Female	16.06 (2.83)	22.25 (4.65)	14.93 (7.48)	22.75 (12.10)	4 MCI 12 AD	6 none 6 one copy 4 two copies
Control sample for delusion of theft	16	Negative score on NPIA and NPIB	73.00 (7.33)	8 Male 8 Female	15.43 (2.34)	21.31 (4.97)	14.93 (6.11)	20.75 (7.31)	2 MCI 14 AD	9 none 5 one copy 2 two copies

Abbreviations. NPIA = delusions; NPIA1 = delusion of harm; NPIA2 = theft, NPIA3 = jealousy, NPIA4 = Capgras syndrome, NPIA5 = phantom boarders, NPIA6 = not recognising one's home; NPIA7 = abandonment; NPIA8 = television/magazine figures present in the house; NPIB = hallucinations; M = mean; SD = standard deviation; MMSE = mini mental state exam; MOCA = Montreal Cognitive Assessment; APOE4 = Apolipoprotein E4.

Table 4.2

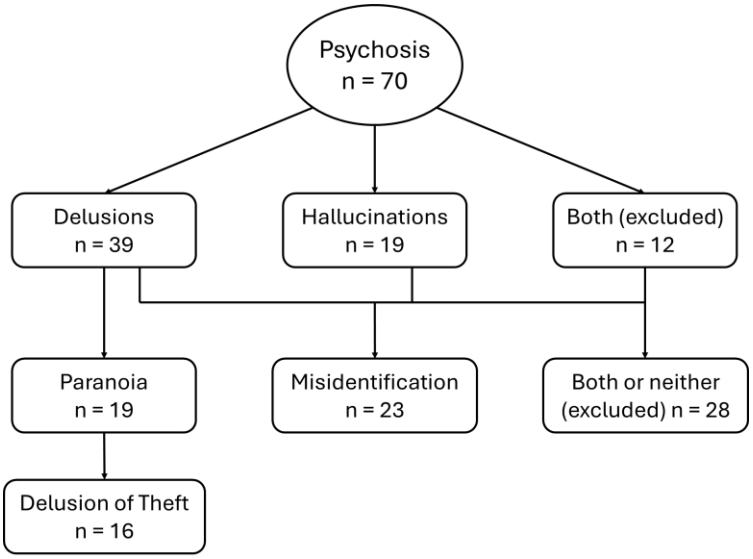
Total numbers of people presenting with delusions and hallucinations subtypes from the NPI

NPI code	Subtype	N tot
NPIA1 (P)	Fear of being in danger/ being harmed	10
NPIA2 (P)	Theft	25
NPIA3 (P)	Jealousy	9
NPIA4 (M)	Phantom boarders (intruders living in the house)	10
NPIA5 (M)	Capgras syndrome	7
NPIA6 (M)	Not recognising one's home	7
NPIA7 (P)	Fear of abandonment	8
NPIA8 (M)	Images from TV or magazines present in the house	2
NPIA9	Other	19
NPIB1	Hearing voices/sounds	12
NPIB2	Talking to people who are not there	5
NPIB3	Seeing people/things not seen by others	20
NPIB4	Smelling odors not smelled by others	3
NPIB5	Tactile feelings	2
NPIB6	Tastes without known cause	1
NPIB7	Other	5

Notes. The total number for each subtypes is derived from the total (psychotic cluster) group. (P) indicates delusions relating to the subtype of paranoia, (M) misidentification.

Figure 4.1

Flowchart for group inclusion



4.4. Results

The descriptive statistics of the sample are presented in Table 4.1, which reports the study and control samples for each group used for the analyses. There were no significant differences found from Welch t-test (for continuous variables) and Chi-square test and Fischer exact test (for categorical variables) between the study and control samples, tested separately for each group and sub-group with respect to disease stage, age, gender, education, neuropsychiatric, neuropsychological, and genetic (APOE4) profile (as shown in Appendix C).

4.4.1. Region of Interest

The analysis of the Region of Interest identified few regions in association with certain sub-groups.

The right orbitalis of the inferior frontal gyrus was a significant predictor in the sub-groups of delusions, paranoia and delusion of theft, as measures of cortical thickness (delusions and paranoia) and cortical volume (delusion of theft) (in order: OR = 0.06 [95% CI 0.00-0.77], p = 0.039 for delusions; OR = 0.00 [95% CI 0.00-0.64], p = 0.048 for paranoia; OR = 1.00 [95% CI 0.99-1.00], p = 0.028 for delusion of theft).

Delusion of theft was also associated with the anterior cingulate cortex (ACC), specifically the cortical volume of the right caudal ACC (OR = 1.00 [95% CI 0.99-1.00], p = 0.045) and the cortical thickness of the left rostral ACC (OR = 0.01 [95% CI 0.00-0.50], p = 0.041).

However, none of these regions survived FDR correction, or Bonferroni correction, based on the number of ROI employed in the analyses (p<.0004) (in Appendix C, the table showing all non-significant results).

No regions were identified for the sub-groups of psychosis considered as a cluster, hallucinations and misidentification.

4.4.2. Voxel-based Morphometry

The brain areas identified from the VBM approach are summarised in Table 4.3, and Figure 4.2 (4.2a shows psychotic cluster, 4.2b delusions, hallucinations and misidentification, and 4.2c paranoia and delusion of theft).

Within the psychotic cluster, significant regions were: the right occipital gyrus at *p*(uncorr)<.001, and in addition to that, the left middle temporal gyrus, the left fusiform gyrus, the right middle frontal gyrus and the left temporal gyrus at *p*(uncorr)<.01.

Within the delusions group, the left medial orbital and right occipital gyri were significant at *p*(uncorr)<.001, and in addition at *p*(uncorr)<.01, the right inferior and middle temporal gyri.

Within the hallucinations group, the left cerebellum was significant at *p*(uncorr)<.001.

Within the sub-group of misidentification, the left cerebellum was significant at *p*(uncorr)<.001, and at *p*(uncorr)<.01 also the right middle frontal gyrus.

In the paranoia sub-group, the right middle frontal at *p*(uncorr)<.001, and in addition the left middle frontal, left superior frontal, and right and left cerebellum at *p*(uncorr)<.01.

Lastly, the right opercularis of the inferior frontal gyrus was significantly associated with delusion of theft at *p*(uncorr)<.001, while the right triangularis of the inferior frontal gyrus at *p*(uncorr)<.01.

Table 4.3

Coordinates of VBM brain areas and labels

Symptom group	Label	Coordinates (x, y, z)	Peak Statistic (z)	*p* (peak level, uncorrected)	Cluster size
Psychotic Cluster	R Occipital	18, -94, 10	3.02	*p*<.001	90
	L Middle Temporal	-64, -56, -14	2.77	*p*=.003	64
	L Fusiform	-34, -40, -10	2.75	*p*=.003	93
	R Middle Frontal	48, 54, -6	2.72	*p*=.003	38
	L Temporal	-58, 12, -18	2.62	*p*=.004	123
Delusions	L Medial Orbital	-16, 22, -30	3.45	*p*<.001	121
	R Occipital	24, -94, 14	3.11	*p*<.001	364
	R Inferior Temporal	62, -24, -34	2.88	*p*=.002	284
	R Middle Temporal	70, -36, -21	2.67	*p*=.004	51
Hallucinations	L Cerebellum	-16, -22, -34	4.22	*p*<.001	136
Misidentification	L Cerebellum	-15, -22, -33	3.66	*p*<.001	267
	R Middle Frontal	28, 18, 30	2.91	*p*=.003	43
Paranoia	R Middle Frontal	28, 16, 28	3.12	*p*<.001	254
	R Middle Frontal	34, 12, 36	2.65	*p*=.004	
	L Middle Frontal	-57, 18, 44	2.85	*p*=.002	55
	L Superior Frontal	-28, 62, 32	2.74	*p*=.003	79
	R Cerebellum	10, -82, -22	2.69	*p*=.004	45
	L Cerebellum	-14, -40, -26	2.68	*p*=.004	67
Delusion of theft	R Opercularis Inferior Frontal	58, 21, 2	3.00	*p*<.001	1054
	R Opercularis Inferior Frontal	51, 15, 10	2.92	*p*=.002	
	R Triangularis Inferior Frontal	51, 30, 4	2.74	*p*=.003	

Notes. Minimum cluster size was set at 25. No region survived FDR and FWE correction. Labels were identified according to the MNI atlas provided within SPM12.

Figure 4.2a

Visual representation of the coordinates derived from the VBM analyses (A: Psychotic Cluster)

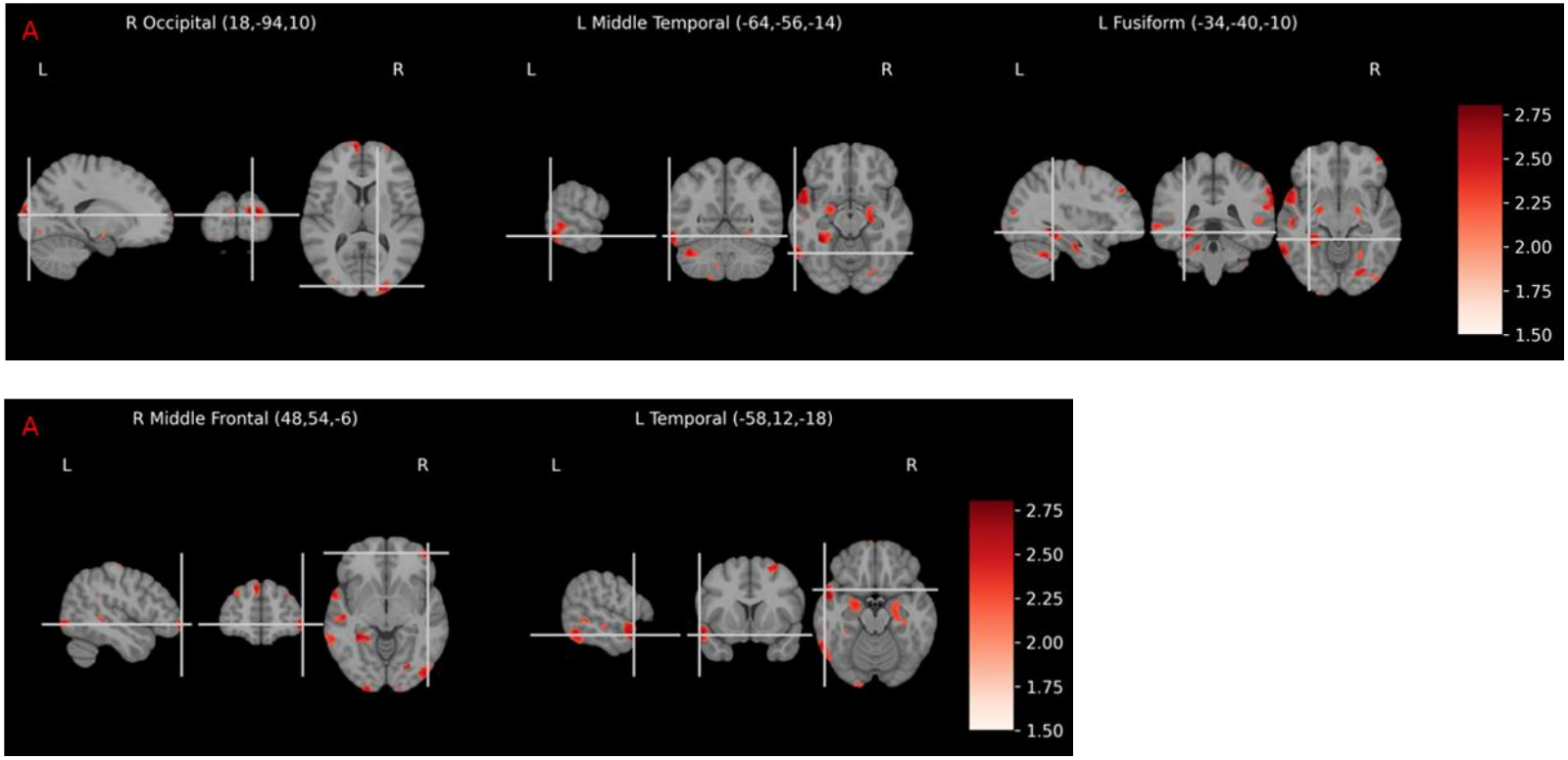


Figure 4.2b

Visual representation of the coordinates derived from the VBM analyses (B: Delusions, C: Hallucinations and D: Misidentification)

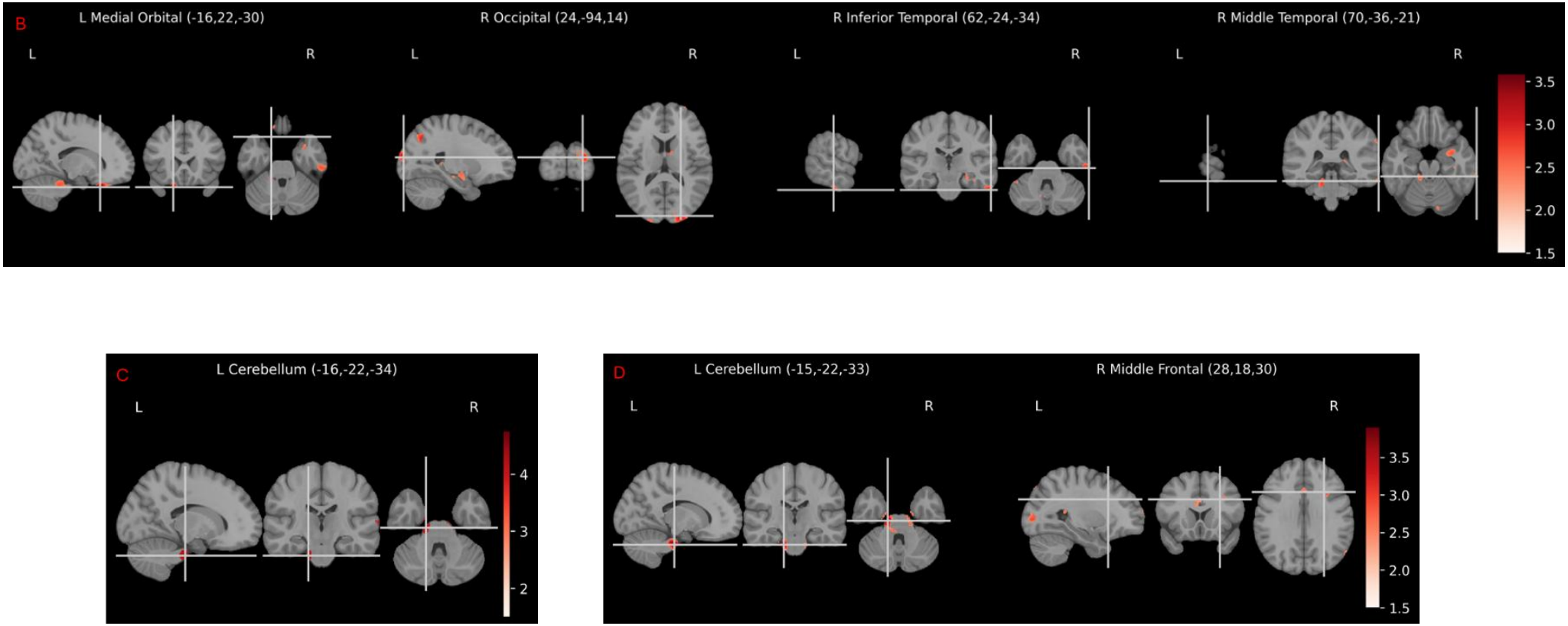
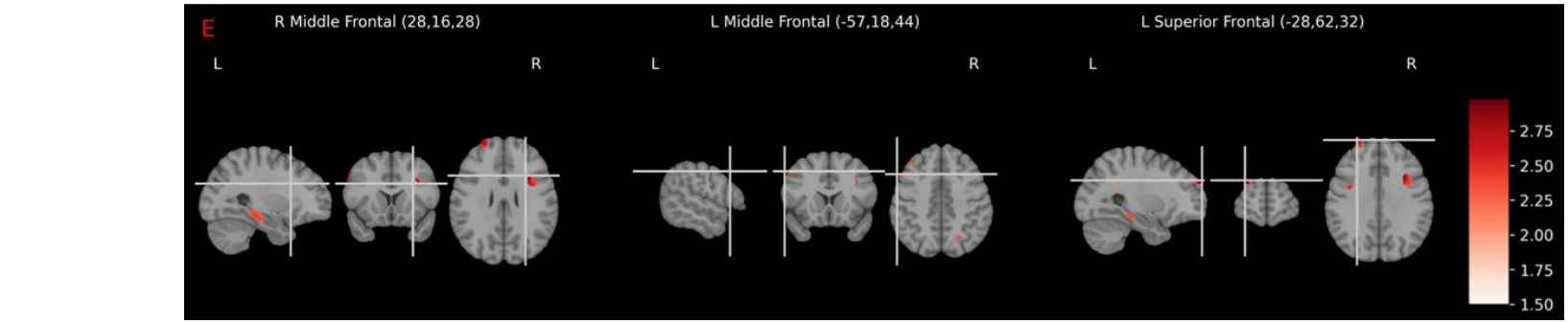
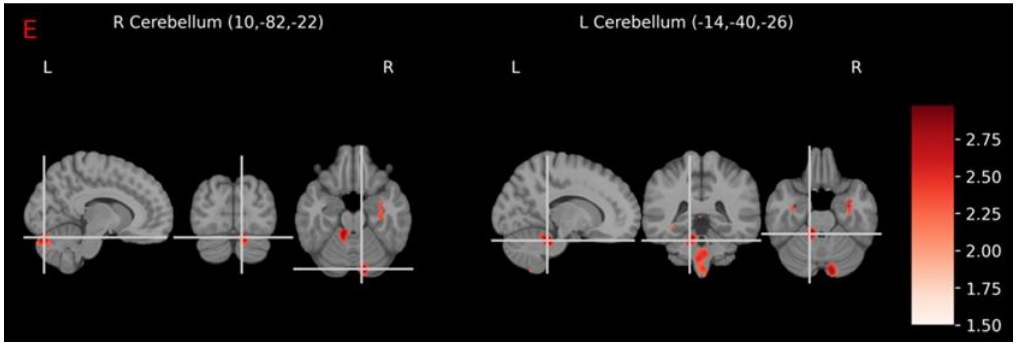
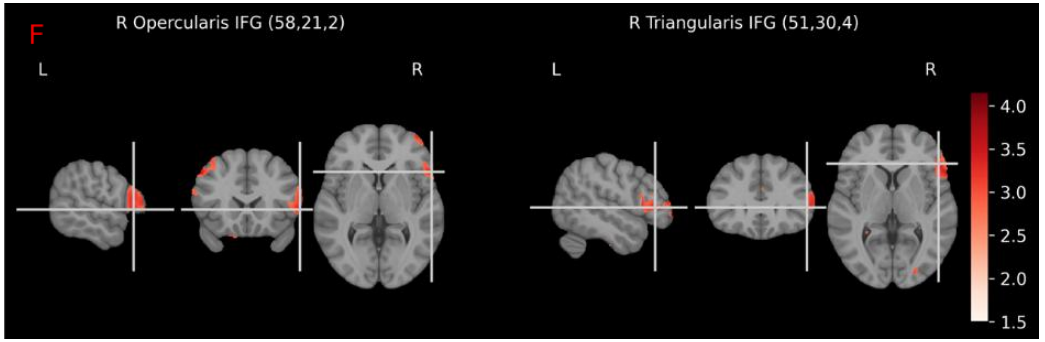


Figure 4.2c

Visual representation of the coordinates derived from the VBM analyses (E: Paranoia and F: Delusion of theft)







Notes. Peak coordinates derived from statistical parametric maps generated in SPM 12 (Ashburner, 2014) were used to produce visualisations of voxel-wise results in Python 3.10.13. Statistical maps (spmT images) were processed using NiBabel and visualised with Nilearn, after restricting analyses to grey matter using a probabilistic tissue mask; results were thresholded at the voxel level. Figures were rendered on a standard MNI template and arranged into multi-panel layouts using Matplotlib. Analyses were conducted within Spyder (version 5.3.3) (Raybaut, 2022) (the code can be found in the OSF Folder linked to this thesis).

4.4.3. Surface-based Morphometry

The brain areas identified from the SBM approach are summarised in Table 4.4 and Figure 4.3. Only within the psychotic cluster, delusions and paranoia groups were significant regions identified, and they were respectively: the left superior temporal gyrus (*p*(uncorr)<.001), the right inferior temporal gyrus and the right lateral orbital gyrus (*p*(uncorr)<.01).

Table 4.4

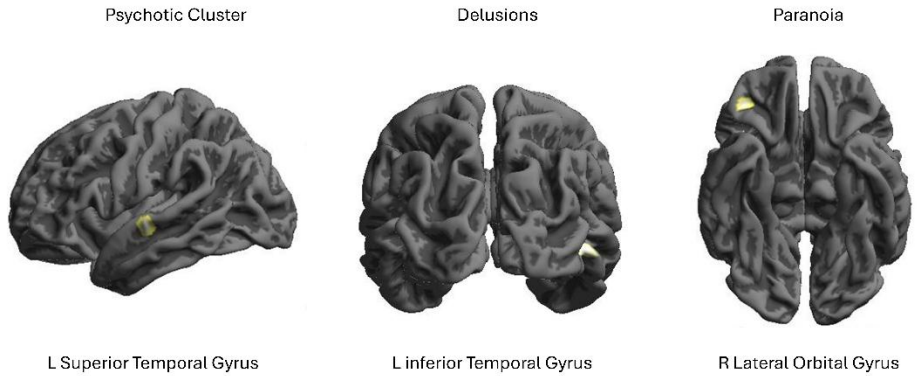
Coordinates of SBM brain areas and labels

Symptom group	Label	Coordinates (x, y, z)	Peak Statistic (z)	*p* (uncorrected)	Cluster size
Psychotic Cluster	L Superior Temporal	-61, -14, -5	2.98	*p*<.001	245
Delusions	R Inferior Temporal	49, -62, -4	2.64	*p*=.004	54
Paranoia	R Lateral Orbital	39 36 -10	2.86	*p*=.004	31

Notes. Minimum cluster size was set at 25. No region survived FDR and FWE correction. Labels were identified according to the MNI atlas provided within SPM12.

Figure 4.3

Visual representation of the coordinates derived from the SBM analyses



Notes. Images were created using SPM 12 (Ashburner, 2014).

4.5. Discussion

To the author's knowledge, this is the first study which investigated the neuroanatomical correlates of psychotic symptoms in AD comparing the results of different neuroimaging approaches and considering the different phenomena underlying this clinical picture. The goal was to provide an overview of the underlying mechanisms of the different manifestations of psychotic symptoms, reducing the influence of potentially confounding variables through the use of matched control samples.

Overall, it appears clear that the use of different types of neuroimaging analysis yields at least partially divergent results, as different areas are found to be significant with the ROI approach compared to the whole-brain VBM and SBM analyses.

4.5.1. Psychotic cluster

When analysing the full sample of participants with psychotic symptoms, slightly different outputs derived from the three methods of investigation. In fact, while the ROI analysis did not evidence any region, the VBM identified one main cluster in the right occipital gyrus, as well as right frontal and left temporal, the latter also evidenced from the SBM.

Overall, the whole brain analyses results are mostly in line with previous studies, which have evidenced regions in temporal (Y.-M. Lee et al., 2021; Misquitta et al., 2020), frontal (Ramusino et al., 2021) and occipital (Banno et al., 2014; Rafii et al., 2014) lobes. As expected, all these areas are also reflected in the analyses of the different aspects of psychotic symptoms, therefore the interpretation of the functions will be carried out below.

4.5.2. Delusions

Among psychotic symptoms, delusions are the type that has been more extensively explored, and many regions across the four lobes have been linked to their manifestation, with a slight predominance of frontotemporal areas in the right hemisphere, and contribution of insula and cingulate cortex. This was partially confirmed in this study.

In confirmation of previous literature, both the VBM and the SBM analyses found clusters in the right inferior temporal (Nakatsuka et al., 2013; Sultzer et al., 2014), while the VBM

identified an additional cluster in the left orbitofrontal cortex (medial) (Qian et al., 2019b). These two areas have been largely linked to delusions, being responsible for the storage and retrieval of biographic memory (Uysal, 2023), for memory and learning processes (Rolls, 2004), assigning values to specific emotional inputs, and the regulation of intentional and motivated behaviours (Rafii et al., 2014). Furthermore, the ROI analysis indicated a link with the inferior frontal gyrus: besides its known involvement in cognitive functions such as attention and executive control (Nakaaki et al., 2013b), the inferior frontal gyrus has been recently proposed in association with consciousness, and specifically the access of conflicting sensory information into conscious experience and selecting what is consciously perceived (Weilnhammer et al., 2021). This might suggest that greater atrophy in these areas could be associated with an inability to correctly access, remember and process information about self and others, which in the absence of the ability to perform a "reality check", to contrast the beliefs and mental imagery with memory for specific events (Sultzer et al., 2014), might contribute to the formation of delusional beliefs.

Lastly, a cluster was identified in the VBM analysis in the right occipital cortex: while this area has been found in association with delusions by some studies (Qian et al., 2019a; Ting et al., 2015), this has been mostly related to misidentification phenomena and hallucinations, linked to misperception and misinterpretation of stimuli (D'Antonio et al., 2019); however this was not the case in this study, as shown in the following section.

4.5.3. Hallucinations and delusions of misidentification

The VBM analysis evidenced the importance of the cerebellum in association with hallucination and the misidentification sub-group, with a small cluster in the frontal lobe only for misidentification. Quite surprisingly, on the other hand, the ROI and SBM analyses did not yield any significant findings. While previous studies on hallucinations and/or delusions of misidentification within Alzheimer's disease do not appear to identify this region as it was seen in chapter 3, cerebellar involvement has been suggested in relation to hallucinations within other syndromes such as Parkinson's disease and Charles Bonnet syndrome (Lawn & ffytche, 2021), schizophrenia (Cierpka et al., 2017) and dementia with Lewy bodies (Zorzi et al., 2021). Furthermore, the cerebellum has also recently come into focus in association with Alzheimer's disease pathology itself, in relation to both motor and nonmotor dysfunctions, including

cognitive impairment, sleep disorders, mood disorders, autonomic dysfunction, and sensory impairment (Yang et al., 2024). Specifically, cerebellar involvement has been proposed in association with impaired executive control, salience detection, episodic memory/self-reflection (Habas et al., 2009) and sensory processing relating to the visual system (Baumann & Mattingley, 2010), all of which appear to be key elements in the hallucinatory and misidentification phenomena in AD (D'Antonio et al., 2021; Zhang et al., 2023). Further investigations might be warranted into the contribution of this brain region.

4.5.4. Delusions relating to paranoia and theft

Within the theme of paranoia, which in this study's sample was almost ubiquitously related to delusions of theft, a predominance of frontal cortical associations was evidenced by the VBM analysis, as well as SBM (paranoia sub-group only) and ROI analysis. Concerning delusions of theft, the VBM evidenced a significant cluster in the inferior frontal gyrus, as was also the case for both sub-groups in the ROI analysis. Previous studies on the paranoid component of delusions have identified this area (Lee et al., 2016; Nakaaki et al., 2013b), while only one study (Nomura et al., 2012) which specifically focused on delusions of theft has found hypoperfusion in the inferior frontal gyrus. As mentioned above, the inferior frontal gyrus has been recently proposed in association with the access of conflicting sensory information into conscious experience and selection of conscious perception (Weilnhammer et al., 2021). It appears that within delusions, associations of this regions are specifically identified in relation to the paranoid theme: this may relate to a difficulty in accurately interpreting external stimuli, which might cause their misinterpretation and consequent delusional (paranoid) state.

In addition to this, the ROI analysis of delusion of theft indicated involvement of the anterior cingulate cortex, which, as seen in chapter 3, has been previously linked to delusions and psychotic symtpoms in general. The anterior cingulate cortex is linked to high-level cognition, such as executive functioning and error detection, and assigning emotion to internal and external stimuli (Boublay et al., 2020; Jeong et al., 2021; Rolls, 2019), suggesting that impaired monitoring of reality functions, associated with abnormal perceptual and emotional experiences, might contribute to the development of delusions.

Lastly, only for the sub-group of delusions relating to paranoid themes, the right lateral orbital region was found from the surface-based morphometry analysis. Greater impairment of the orbitofrontal cortex is consistent with the general literature on delusions, as seen above (Sultzer et al., 2014; Tetreault et al., 2020), and particularly one study on paranoid delusions (Whitehead et al., 2012) indicated this area, linking it to failures in social reasoning centres, and wrongly assigning emotional or social significance to everyday non-threatening social stimuli.

4.5.5. Limitations

A few important considerations must be made which constituted limitations in this study. A common issue in studies on psychotic symptoms in AD is the availability of sample size. Despite using a large international database such as ADNI, this is still an issue when considering the different thematic content. Furthermore, based on the efforts to maximise the sample size, this was heterogeneous with respect to disease stage, as participants with MCI due to AD were included, as well as participants with AD dementia at different disease severity. While this was accounted for with appropriately matched control samples, larger sample size would allow future investigations to stratify the sample to account for severity of disease. It is also possible that the close matching of controls which included neuropsychiatric score might have influenced the results by including in the control sample participants with other neuropsychiatric symptoms that are linked to certain brain regions including for example, as seen in Table 1.1 the anterior cingulate cortex. An alternative method of controlling symptomology statistically could be taken in the future to contrast the findings.

Pertaining the ADNI dataset, is primarily composed of white, very high education participants with high socioeconomic status, therefore the findings of this study should be carefully considered with respect to generalisability.

Another limitation to consider pertains to the tool that is employed to classify psychotic and other neuropsychiatric symptoms, as discussed in previous chapters: ADNI's protocol employed in this study relies on the Neuropsychiatric Inventory (Cummings et al., 1994) administered every 12 months (with a reflection over a period of the previous 4 weeks); while the NPI is considered a valid tool, it is possible that a more frequent collection of data might lead to a more precise assessment, and to a clearer picture

particularly of the thematic subtypes. This, in turn, would have the potential to allow for larger, and more accurate, pools of participants for future investigations, as at the yearly assessments performed within the ADNI protocols, some of the information pertaining to the symptoms' fluctuations might be missed.

4.6. Conclusions

Our findings indicate that certain brain areas such as the fronto-temporal areas link to most psychotic phenomena, while others appear to be related to specific themes, such as a frontal predominance in association with paranoid and theft delusions, and an involvement of the cerebellum in relation to hallucinations and delusions of misidentification. Furthermore, overlap in the findings between the different techniques was only partially present, providing support for the notion of employing complementary approaches. It would appear that in the context of identifying brain areas that link to psychotic phenomena, focusing on one specific theme rather than considering the whole cluster of symptoms, might yield clearer results, and allow for specific interpretation of the experience of these symptoms, eventually having the potential to lead to tailored targeted treatments. While some progress has been made in this direction, further studies are needed, particularly with expanded sample sizes, which will allow for disease stage stratification, in order to clarify these findings.

Chapter 5 - The role of cognitive functions in the manifestation of psychotic symptoms in Alzheimer's disease: a systematic review

5.1. Overview

In chapter 1 it was highlighted that psychotic symptoms are associated with greater cognitive decline and a detrimental impact on disease trajectory; some key associations have been identified with specific cognitive functions, such as memory, attention, executive and visuospatial functions, which have also been introduced in chapter 3 with respect to the link between brain areas and cognitive functions in explaining psychotic symptoms. It has been outlined that while there appears to be consensus across the literature on the relation between the presence of psychotic symptoms and overall cognitive decline, clarity is still needed on the role of specific cognitive functions as, similarly to the study of brain areas synthesised in chapter 3, a large body of literature over the past few decades has investigated the association between cognitive functions and specific manifestations of psychotic phenomena producing variable results, which have not been systematically synthesised so far. Therefore, addressing objective 4 of this thesis in a complementary manner to chapter 3 which focused on neuroanatomical associations, this chapter presents a systematic review which has the aim of providing a synthesis of all studies that have investigated associations between specific cognitive functions and different manifestations of psychotic phenomena in AD dementia and MCI. The protocol for this review, similarly to chapter 3, was created according to PRISMA guidelines (Page, McKenzie, et al., 2021; Page, Moher, et al., 2021), and it was pre-registered on OSF (https://osf.io/jw5cu/). Searches were performed on PubMed, PsycInfo and Web of Science, and they led to the selection of forty-three papers. In this chapter, a synthesis will be provided outlining the cognitive domains and processes that were found to associate with psychotic symptoms according to different means of classification. Specifically, psychosis was analysed as a cluster in seventeen studies overall, yielding associations mainly with measures of executive function and working memory, and to a lesser extent episodic and semantic memory and language. Delusions were investigated in sixteen studies, mostly identifying associations with measures of executive function and episodic memory, and also spatiotemporal orientation and semantic memory. Eight studies focused on hallucinations, which were mostly found to associate with attention, language, executive function, as well as episodic memory.

Lastly, twelve studies focused on thematic subtypes of misidentification and paranoia: of these, nine studies analysed the theme of misidentification (inclusive of delusions of misidentification and hallucinations), and ten paranoia (inclusive of delusions relating to paranoid themes such as theft, abandonment and jealousy). Individuals presenting with misidentification had overall greater impairments, particularly in visuospatial function, attention, episodic and semantic memory, as well as executive function; those who manifested paranoia, in episodic and semantic memory. Finally, these findings are discussed, focusing on the implications for future research that considers associations between cognitive functions and different manifestations of psychotic phenomena.

5.2. Introduction

In chapter 1 it was discussed that neuropsychiatric symptoms, and specifically psychotic symptoms in Alzheimer's disease (AD) are interrelated with cognitive symptoms at several levels. It was shown how the presence of Mild Behavioural Impairment (Ismail et al., 2017) (MBI) is associated with worse cognitive performance (Rouse et al., 2021; Yoon et al., 2022), and that specifically psychotic symptoms at earlier stages of disease (Van der Mussele et al., 2013) are associated with a more rapid cognitive (Almeida et al., 2024; Ropacki & Jeste, 2005) and functional (Fischer et al., 2012) decline, as well as greater cognitive dysfunction and dementia severity (Connors, Ames, et al., 2018; Fuller et al., 2019). At the same time, investigations into the risk factors of psychotic symptoms in Alzheimer's disease have identified that greater cognitive dysfunction is present in individuals who will later develop psychotic symptoms (Paulsen, Salmon, et al., 2000; Weamer et al., 2009), thus suggesting a complex interaction between psychotic manifestations and cognitive functions.

Delving deeper into the different domains of cognition, an interesting area of research has focused on specifying the associations between psychotic symptoms and specific functions and processes, thus going beyond generalised neuropsychological functioning, as illustrated through, for example, cognitive screening tests. This has been partially explored in the discussion of chapter 3, whereby greater atrophy in specific brain areas, such as the right frontal lobe, the anterior cingulate cortex, and temporo-occipital areas, has been found in association with different manifestations of psychotic phenomena, and an interpretation was provided, linking the cognitive functions that are typically associated with those brain regions with the manifestation of psychosis. This

issue has been tackled by a substantial number of studies in the past three decades; however, their findings are not always consistent (Murray et al., 2014; Reeves et al., 2012), likely due to the vast heterogeneity of methodology employed, particularly in relation to the neuropsychological assessment. To date, no review exists which synthesises the findings of such studies in a systematic way, considering all manifestations of psychotic phenomena, as well as interpreting elements relating to study design that have the potential to affect findings. Therefore, the focus of this chapter will be that of providing a systematic review and synthesis of all studies that have investigated the role of specific cognitive functions as potential risk factors for the manifestation of psychotic phenomena.

5.2.1. Cognitive functions and assessment methods

As mentioned in the previous section, one thing to consider when approaching the study of cognition within Alzheimer's disease is the heterogeneity of neuropsychological assessment, spanning from individual tests like the historical Clock Drawing Test (Goodglass et al., 1983) and Trail Making Test (Partington & Leiter, 1949; Reitan, 1955), or the popular Verbal Fluency Test (Rosser & Hodges, 1994), to cognitive screening instrument such as the mini mental state exam (MMSE) (Folstein et al., 1975), typically used to assess global cognition and disease severity, and test batteries such as the Alzheimer's Disease Assessment Scale (ADAS-Cog-13) (Mohs, 1994), frequently employed as outcome measure in clinical trials (Harrison, 2022). As it was previously mentioned in chapter 1, while introducing the cognitive functions which are impacted in AD, for many years episodic memory was considered a central symptom, and consequently, tools such as the ADAS-Cog-13 are heavily oriented toward the assessment of episodic memory, which comprise the majority of the total scoring (Harrison, 2022). However, it was discussed how other functions are now understood to be affected at earlier as well as later stages of disease, among which for example semantic processing (Venneri et al., 2019), executive function (Tenchov et al., 2024; Testo et al., 2025) and visuospatial function (Salimi et al., 2018). Therefore, it has been suggested that the use of cognitive assessment in Alzheimer's disease should be carefully considered, with the employment of batteries with sufficient cognitive coverage (Harrison, 2022). Importantly, in chapter 1, and also in chapter 3, it has been highlighted how a profile of impairment on different cognitive functions (i.e., not

primarily amnestic) tends to be associated with greater neuropsychiatric (Chen et al., 2021) and psychotic (Agüera-Ortiz et al., 2022; Almeida et al., 2024) load.

Therefore, as it is expected that a greater number of studies will focus on episodic memory compared to other functions, an analysis of the proportion of significant findings will be proposed, rather than only considering the total of significant associations with a specific function (similarly to what done in chapter 3, whereby it was discussed the brain areas identified compared to the brain areas investigated), in order to effectively synthesise the findings of the correlates of psychotic symptoms in AD.

Furthermore, it is important to note the types of tests that were used in relation to how these were interpreted, as while some types of tests are specifically designed to heavily rely upon one cognitive function, or a specific process, others bridge different cognition domains (Harvey, 2019). It is important to note that this is expected to happen: in his paper on domains of cognition, Harvey (2019) highlights that the intercorrelation between cognitive functions does not undermine their construct validity, it is rather a reflection of the natural intercorrelation between functions.

In the next sections, an overview of the cognitive domains, sub-domains and processes is provided, and the main neuropsychological assessments used to study each function in this population is indicated, noting the instances where tests are used and interpreted in relation to more than one function.

5.2.1.1. Memory

Memory is one of the most complex domains, as it presents with multiple sub-domains, each functioning on specific processes and relating to distinct brain mechanisms and thus presenting with different levels of impairment within the AD pathology (Lezak et al., 2012). Historically, episodic memory has been given greater attention in the research in Alzheimer's disease, compared to all other functions, as it is considered a hallmark of AD (Launay et al., 2023), and it features among its diagnostic criteria (Dubois et al., 2014). Unsurprisingly, assessment scales such as the ADAS-Cog-13 previously described heavily rely in their subcomponents on measures of episodic memory (Harrison, 2022), specifically the abilities of encoding (i.e. learning), storing, recall (without cues) and recognition (with cues). Examples of the types of tests used within AD assessment of the ability to learn and remember information are the Hopkins Verbal

Learning Test (Brandt, 1991), the California Verbal Learning Test (Delis et al., 1987), the Rey Auditory Verbal Learning Test, as well as tasks of immediate and delayed recall and recognition present in most neuropsychological batteries, such as the ADAS-Cog-13, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998), or the Wechsler Memory Scale (WMS) (Wechsler, 1987, 1997). An important distinction to be made concerns the sense through which new information is acquired; typical tests described above tend to focus on verbal (auditory) memory, however visual memory is also an important function to assess, through tests such as the Benton Visual Retention Test (Benton, 1945), or tests which requires drawing from the recall of a complex figure previously copied, such as the Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944; Rey, 1941), or the figure copy task that is included for example in the RBANS (Randolph et al., 1998), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Fillenbaum & Mohs, 2023) or in the Mattis Dementia Rating Scale (DRS) (Jurica et al., 1988).

Semantic memory is the cognitive system that stores general world knowledge about concepts, facts, word meanings, people, objects, actions, and relations—knowledge (Jones & Avery, 2019). Semantic memory and semantic processing are typically assessed in AD and dementia with tests such as the category verbal fluency test. This test assesses the ability with which words can be generated in response to a semantic stimulus (the stimulus can also be phonemic, however this other type of verbal fluency test will be explained when introducing executive function, as it relates more to that domain (Wright et al., 2023)). Assessment consists in producing as many words as possible in a set period of time, belonging to a category, for example "animals" (Benton, 1968), thus relying on semantic memory as well as language (Wright et al., 2023).

A core aspect related to memory that is affected by AD dementia is spatial and temporal orientation: this is normally assessed within clinical batteries such as the MMSE and ADAS-Cog-13, with questions relating to the year, season, month, current date and day of the week, as well as country, city, and location such as address, type of building and room.

In addition to long-term memory, short-term memory, i.e., the temporary storage of information which can be verbal or visual, is also typically impaired in AD dementia. The ability to hold information in consciousness for adaptive use is referred to as working

memory, which again can include information within a verbal and visual modality. Information can be transferred from short-term and working memory to long-term storage, in a process requiring either active processing or salience of the stimulus in order for it to be effectively encoded (Harvey, 2019). While short-term memory refers to the ability of storing information for a brief period of time, working memory implies the manipulation of information (Baddeley & Logie, 1999), and as such, aspects of working memory are core components of executive function (see below). Typical assessments of these functions are the digit span forward and backward, respectively (Wechsler, 1987, 1997). Tests described above in the encoding task (e.g., learning a list of words, only in the "immediate recall" part of the test) also rely to a certain degree upon short-term and working memory.

5.2.1.2. Other cognitive functions: language, attention, processing speed, executive function, visuospatial function and motor skills

Language skills include receptive (comprehension) and productive (expression) abilities. Verbal comprehension is normally examined using single words, commands, statements and sections (Lezak et al., 2012); an example of this is the Token Test, in which the examiner gives spoken commands of increasing length and grammatical complexity using a set of tokens (De Renzi & Vignolo, 1962). The most common assessment of verbal expression refers to the ability to name objects or pictures, among which the most commonly used test is the Boston Naming Test (Goodglass et al., 1983) (also included in batteries such as the CERAD dementia battery (Fillenbaum & Mohs, 2023)), or similar tests of confrontational naming as included for example in the RBANS.

The assessment of attention is typically reflective of the two core sub-domains of selective (or divided) attention, and sustained attention (also referred to as vigilance, or concentration) (Harvey, 2019). Selective attention refers to discriminating between relevant and irrelevant information, and a typical test is the Digit Cancellation Test (Sohlberg & Mateer, 1989), as well as the Stroop Test (Stroop, 1935) that is discussed below as it is also and typically used to test executive function. Sustained attention, on the other hand, is normally assessed using tasks that involve the sequential presentation of stimuli over a period of time, with instruction to indicate when the target stimulus is perceived (Lezak et al., 2012). While some tests are specifically designed to

put a heavy demand on this function, it should be considered that many cognitive tests require attention (Lezak et al., 2012).

Processing speed refers to the speed required to process a task and thus perform it as rapidly as possible; as such, similarly to attention, it underlies tests for other cognitive functions, and it tends to be indicative of overall cognitive performance (Harvey, 2019). It is typically assessed via relatively simple tests, such as part A of the Trail Making Test (connecting a series of number in ascending order) (Partington & Leiter, 1949; Reitan, 1955), or the Digit Symbol Substitution Test (matching symbols to numbers) (Wechsler, 1981), where the critical features is time elapsed, alongside correctness of performance; both tests are also used to measure attention.

Under the domain of executive functioning fall all the processes relating to effectively using cognitive resources to solve problems efficiently and plan for the future. Thus all functions relating to problem solving, planning, updating, ability to inhibit behaviour and resist impulses, cognitive flexibility and the abilities of identifying patterns and abstract reasoning relate to this domain, as well as working memory (described above) (Uysal, 2023). Executive function has been primarily conceptualised as encompassing a range of various complex cognitive processes and sub-processes (Elliott, 2003; Tsuchida & Fellows, 2013). One theoretical framework to characterise executive function is to consider a hierarchical model in which there are three base core functions: inhibition, comprising of inhibitory control, and interference control; working memory (as seen above), which includes updating; cognitive flexibility, also referred to as mental set shifting/switching, which supports creativity. Starting from these, it is possible to build the higher-order executive functions such as reasoning, problem solving and planning (Diamond, 2013). The capabilities that relate to executive function enable a person to engage successfully in independent, purposive, self-directed, and self-serving behaviour, and impairments in this domain tend to present globally, therefore affecting all processes indicated above (Lezak et al., 2012). Classic tests of executive function tend to focus on specific sub-components; for instance, the Stroop Test (Stroop, 1935), which assesses the ability to inhibit cognitive interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus (Scarpina & Tagini, 2017); part B of the Trail Making Test, assessing switching, as it requires continuously changing from number to letter (in

ascending/alphabetical order); the Wisconsin Card Sorting Test (WCST) (Berg, 1948; Grant & Berg, 1948) whereby participants must adapt to changing card sorting principles (based on key stimulus cards which differ with respect to colour, shape and number) based on the examiner's feedback which requires cognitive flexibility, abstract reasoning and the ability to shift problem solving strategies; the phonemic fluency test, mentioned above in the section on semantic memory, such as the Controlled Oral Word Association Test (COWAT) (Benton et al., 1994) requires updating and monitoring of working memory and inhibition of incorrect responses, as it consists of generating as many words as possible in a set period of time starting with a specific letter.

Within the domain of visuospatial function, it is important to distinguish between visual perception and visuoconstructional skills. Visual perception refers to the processing of visual information; one example of assessment method is the Visual Object and Space Perception Battery (Warrington et al., 1991). More widely investigated within AD, however, are visuoconstructional skills. These are at times referred to as visuoconstructional praxis, however in below it is explained what pure praxis is and how it is assessed (Lezak et al., 2012). Visuoconstructional ability is normally assessed within AD through drawing, either free, such as the case of the Clock Drawing Test (Goodglass et al., 1983) or copying, with the most common being Clock copy, or the copy task of the Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944; Rey, 1941); while drawing from recollection relates most to visual memory, it is at times considered among visuospatial function.

Motor skills include different elements of fine motor abilities, such as manual dexterity, motor speed, and reaction time, and more global skills such as balance. One test of manual dexterity is the Grooved Pegboard Test (Klove, 1963). Praxis, on the other hand, refers to the ability to plan and carry out purposeful, learned actions, and as such it requires the knowledge of how to use movement to achieve a goal; apraxia (impaired or loss of praxis) is therefore defined as a state of inability to carry out a learned motor act (Chandra et al., 2015). Apraxia occurs frequently in AD and it is associated with disease severity, affecting the independent functioning and communication, resulting in impaired activities of daily living (Vakkila & Jehkonen, 2023). It consists of two, interrelated components, one referring to the motor plans and production of skilled movement (ideomotor), and one referring to the knowledge about the action plan and

seriation of actions into a sequence (conceptual/ideational). Batteries like the ADAS-Cog-13 and the Cambridge Cognition Examination (CAMCOG) include items meant to assess this function; more generally, testing for apraxia typically includes imitation of the examiner who either makes symbolic or communicative movements, or uses objects/pantomimes, as well as command for each of these kinds of activity (Lezak et al., 2012).

5.2.2. Rationale and aim

Considering the established relationship between psychotic and cognitive symptoms in AD, a substantial body of research has focused on the efforts of clarifying which specific cognitive functions can be linked with these symptoms. Despite this, no review to date has systematically and comprehensively synthesised the findings, considering the potential impact of factors like the heterogeneity of assessment tests and batteries, the specific manifestation of psychosis investigated, as well as the interpretation of which cognitive function a certain test is assessing. In fact, a few systematic reviews (e.g., those mentioned in chapter 1, including Chatzikostopoulos et al. (2025); Chen et al. (2021); Rosenberg et al. (2015)) have focused on all neuropsychiatric symptoms, as well as neuroanatomy, and did therefore not have the scope to provide a specific overview on all cognitive functions in relation to the different psychotic manifestations.

Similarly, reviews such as Murray et al. (2014) or Ballard (2024) which synthesised the findings of psychosis, or Reeves et al. (2012) which focused on delusions, were approached with a focus on several features such as neuroanatomy, neurobiology, genetics, as well as cognition, therefore did not have the opportunity to capture and analyse the entire body of evidence in relation to this more focused review.

Based on these considerations, the aim of this review is to provide a clear and comprehensive summary and synthesis of the cognitive functions that have been found to be associated with psychotic symptoms, broken down into different subtypes, extracting data that has the potential to influence and impact such findings, such as sample size, disease stage, psychosis assessment tool and neuropsychological assessments used.

5.3. Methods

The protocol for this systematic review has been pre-registered on the Open Science Foundation (OSF), and it has followed the PRISMA updated guidelines (Page, McKenzie, et al., 2021; Page, Moher, et al., 2021) for systematic reviews.

5.3.1. Eligibility criteria

Eligibility criteria were similar to those applied in chapter 3. Studies were considered eligible if they performed primary or secondary data analysis to investigate the cognitive functions in correlation and/or as predictors of psychotic symptoms in AD. Studies which only focused on general cognitive decline (e.g., using cognitive screening scales as a measure of global cognitive function) were not included in the study, if they did not investigate the role of specific cognitive functions in relation to psychosis. Both cross-sectional and longitudinal studies were included (the latter focusing on the cognitive functions as predictors of later development of psychotic symptoms). Studies were considered eligible if they contained samples of people with Alzheimer's disease and/or Mild Cognitive Impairment, with a focus on psychotic symptoms as a cluster, delusions and/or hallucinations. Studies were also included if they focused on neuropsychiatric symptoms in general, inclusive of delusions and/or hallucinations as a components. Lastly, results were limited to publications in English and peer-reviewed publications, with no restrictions on publication date.

5.3.2. Search sources and strategy

The searches were performed from the 18th to the 31st of January 2022, using PubMed, Web of Science and PsychINFO. Furthermore, the reference list of any included study was reviewed to find additional relevant publications that might have been missed in the database search, as well as the reference list from other reviews which focused on a similar topic.

The following terms were used in the database searches:

"Psychosis" OR "Psychotic" OR "Neuropsychiatric" OR "NPS" OR "behavioural" OR "behavioral" OR "BPSD" OR "Delusion*" OR "Hallucination*" OR "Misidentification" OR "Persecut*" OR Capgras"

AND

"Alzheimer*" OR "AD" OR "Mild Cognitive Impairment" OR "MCI"

AND

"Cognit*" OR "Neuropsycholog*" OR "Executive" OR "Memory" OR "Attention" OR "Language" OR "Processing Speed" OR "Verbal" OR "Visu*"

AND

"Corr*" OR "Relat*" OR "Associat*" OR "Predict*"

All records retrieved were imported into an Endnote library, where duplicates were removed automatically (through Endnote import procedure), and manually by the researcher. The titles and abstracts of all search results were screened against the inclusion criteria. In cases where the record (title and abstract) did provide enough information to assess whether the study should be included, the report was passed to the next stage, where the full texts were examined. The full texts of all reports that appeared to meet the inclusion criteria (along with those where a decision could not be made at the screening stage) were then individually examined for eligibility by two independent reviewers, with a third independent reviewer from the research team helping to resolve any discrepancies as to which articles should be included. The article selection process, as well as the number of articles excluded at each stage, was documented in a PRISMA flow diagram (Figure 5.1).

5.3.3. Quality assessment

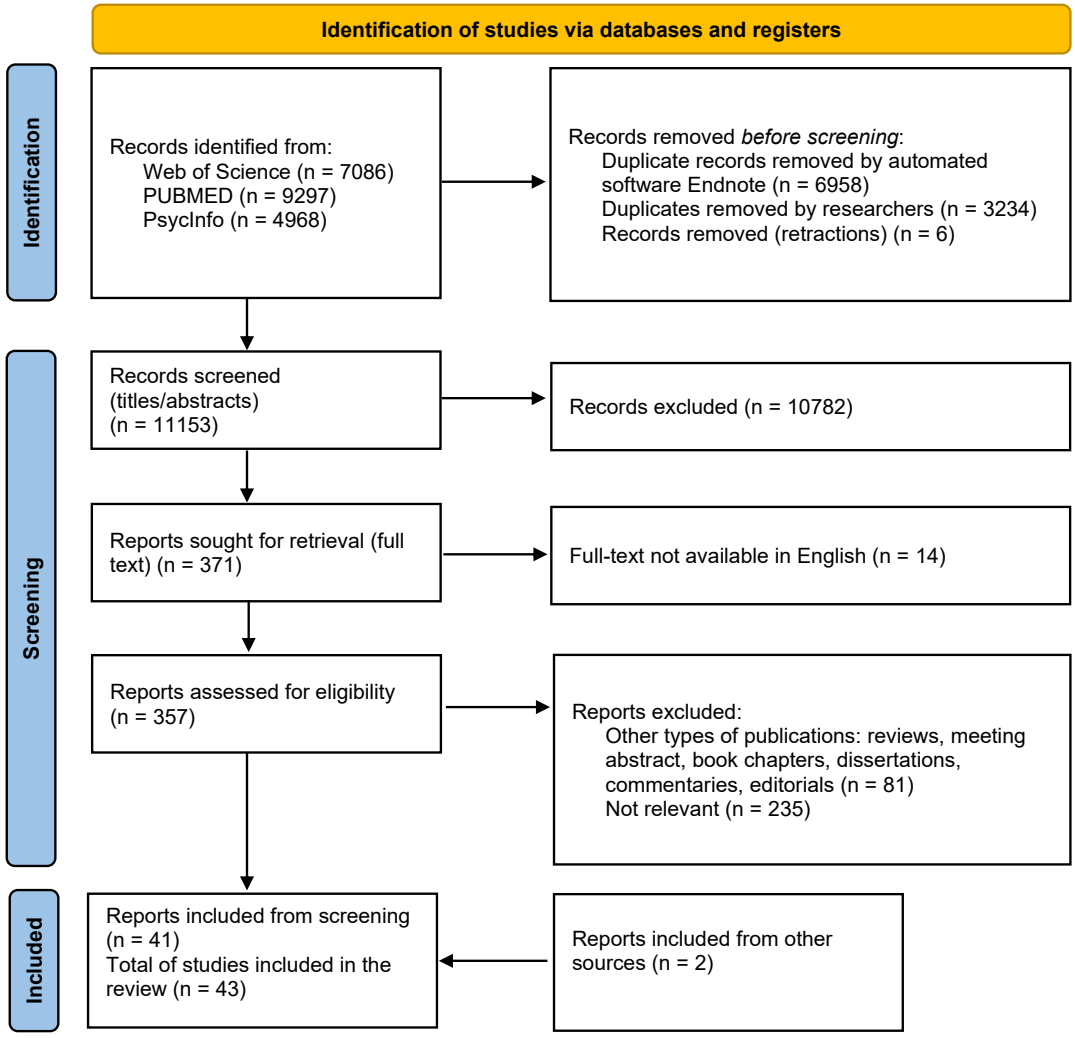
The papers included in the review were assessed for risk of bias, using the same validated tool that was used for the systematic review on neuroanatomical correlates and predictors of psychosis in chapter 3, the Joanna Briggs Institute Critical Appraisal Tool Checklist for Analytical Cross-Sectional Studies (Joanna Briggs Institute, 2014) (see Appendix B for reported Checklist and instructions for application).

These were applied to each study by two independent reviewers, with the purpose of assessing their methodological quality, and determining the extent to which the possibility of bias was addressed in their designs and analyses.

Any case of discrepancy between the two reviewers was resolved through discussion, and agreement on the score of all items was reached.

Figure 5.1

Prisma flowchart



5.3.4. Data collection and extraction

Data from each article was extracted by two independent reviewers, and any discrepancies were discussed and resolved by a third reviewer. A protocol for extracting data was designed, that would allow synthesis, with clear characterisation of study design, participants, symptom studied, and cognitive features. Specifically, the

following headings were used[1]: Author and Publication Year; Symptom(s) Investigated; Participants; Study Design(s); Aim(s); Confounding Factors; Cognitive Function(s) Investigated; Neuropsychological Assessment; Statistical Threshold and Corrections; Relevant Findings (further divided into two columns, one extracting the findings as reported in the study, and one to identify the relevant cognitive function(s)).

5.4. Results

5.4.1. Holistic overview of the main findings

From the screening process, forty-one papers were selected, and two were added from reviewing the reference lists of relevant studies and reviews (Figure 5.1). Data was extracted from the total forty-three papers according to the above-mentioned protocol, which highlighted a moderate upward trend in number of publication per year, much less evident than the one found in studies on neuroanatomy as seen in chapter 3, with nine papers published between 1991 and 2000, sixteen between 2001-2010, and lastly eighteen between 2011-2020.

The majority of studies had a cross-sectional design, with only twelve performing longitudinal analyses.

Diagnosis of probable or possible Alzheimer's disease was performed according to the NINCDS-ADRDA criteria (McKhann et al., 1984) in most studies, with two exceptions, in which the assessment was carried out by clinicians and not otherwise specified. Nine studies in total used the DSM (American Psychiatric Association, 1980, 1994, 2000) either as sole diagnostic criterion (n=2), or in support of the NINCDS-ADRDA criteria (n=7); MMSE (n=4) and/or CDR (n=3), and in one case Petersen's criteria for MCI assessment (Petersen, 2004) were also used in support of the NINCDS-ADRDA criteria. The majority of studies focused on AD, with no further stratification based on disease severity except in two of these, and only four studies included a mix of participants with AD dementia and MCI; four studies included dementias due to other aetiology than AD.

[1] Similarly to chapter 3, for better readability of the table, additional columns reporting information on AD diagnosis (specifying criteria used) and disease stage, and symptom rating scale or assessment method used for psychotic symptoms are only included in the digital version of this table, available in the OSF folder, however summaries of this information are available in the results section of this chapter.

Assessment of psychotic symptoms was mostly based on rating scales: the Neuropsychiatric Inventory (Cummings et al., 1994) was the most commonly used (n=19) followed by the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al., 1987), used in six studies; the Behavioural Rating Scale for Dementia from the Consortium to Establish a Registry for Alzheimer's Disease (BRSD CERAD) (Mirra et al., 1991; Morris et al., 1989; Tariot et al., 1995) was used in four studies; the Launay-Slade Hallucinations Scale (Launay & Slade, 1981) was used in three; two studies used the Dementia Psychosis Scale (Migliorelli et al., 1995), one the Neurobehavioral rating scale (Levin et al., 1987), one the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD) (Devanand et al., 1992). Six papers reported clinicians conducting the assessment through semi-structured interviews, questionnaires, or applying clinical judgement, and in four of these studies, the diagnosis of delusions and/or hallucinations was based on DSM (American Psychiatric Association, 1980, 1987) definitions . Only in one study the assessment method was not specified.

In terms of the phenomenology of the psychotic symptom investigated, sixteen studies performed investigations on delusions; six of these had wider scope of also performing separate analyses on other neuropsychiatric symptoms such as hallucinations, or psychotic cluster, while nine only focused on delusions, normally without consideration in their analyses of other neuropsychiatric symptoms including hallucinations (those that did were explicitly mentioned in the confounding factors column of the relevant tables of results); of these nine, one further performed separate analyses on specific themes (see below). Only two studies (by the same author) focused only on hallucinations, while five performed separate investigations on both delusions and hallucinations and one on hallucinations, psychotic cluster and thematic subtypes (see below), for a total of eight studies which included analyses on hallucinations (similar to delusions, without considering the presence of other neuropsychiatric or psychotic symptoms in their analyses, and if this information was available it is made clear in the confounding factors column of the tables of results). Seventeen studies performed analyses on psychosis as a cluster (in one of these, the cluster was also inclusive of aberrant motor behaviour, and in another one of aberrant motor behaviour and agitation). Lastly, twelve studies focused on the analyses of the subgroups formed by misidentification and paranoia (two of these in addition to the analyses on the groups

formed by the two themes, also performed analyses on psychosis as a cluster, and one separated hallucinations and delusions of misidentification therefore performing separate analyses for all the different groups); within these twelve studies, three only investigated delusions relating to paranoia (two of these only delusions of theft) and not misidentification; two studies only focused on delusions of misidentification/Capgras syndrome, and not paranoia; seven performed separate analyses, grouping participants based on both thematic subtypes of paranoia and misidentification.

Sample sizes in relation to the participants presenting with the symptoms of interest varied from two to one-hundred-fifty-five. However, some of the studies did not report the proportion of participants presenting with the symptoms of interest, rather only that of possible/probable AD patients and healthy controls, therefore this element cannot be reported with certainty.

Only four studies did not report any significant findings, however twelve studies focused on more than one manifestation of psychotic phenomena, and in many occasions some of these associations were not significant; for example, of the five studies that focused on both delusions and hallucinations as individual symptoms, one found significant patterns of associations with both symptoms, two only found significant associations with hallucinations, and one only with delusions. A similar pattern was shown in the studies that distinguished between paranoia and misidentification, one of which found only significant associations with paranoia while three only for misidentification. Furthermore, importantly the threshold for significance varied, from uncorrected $p<.05$, to $p<.001$ and p values based on Bonferroni's correction for multiple comparisons.

Lastly, only half of the studies explicitly accounted for covariates or confounding factors in their analyses; these were mostly age (n=18), education (n=16), overall cognitive ability mainly using MMSE (n=12), gender (n=9) and duration of illness (n=6).

5.4.2. Synthesis of neuropsychological assessment and cognitive functions

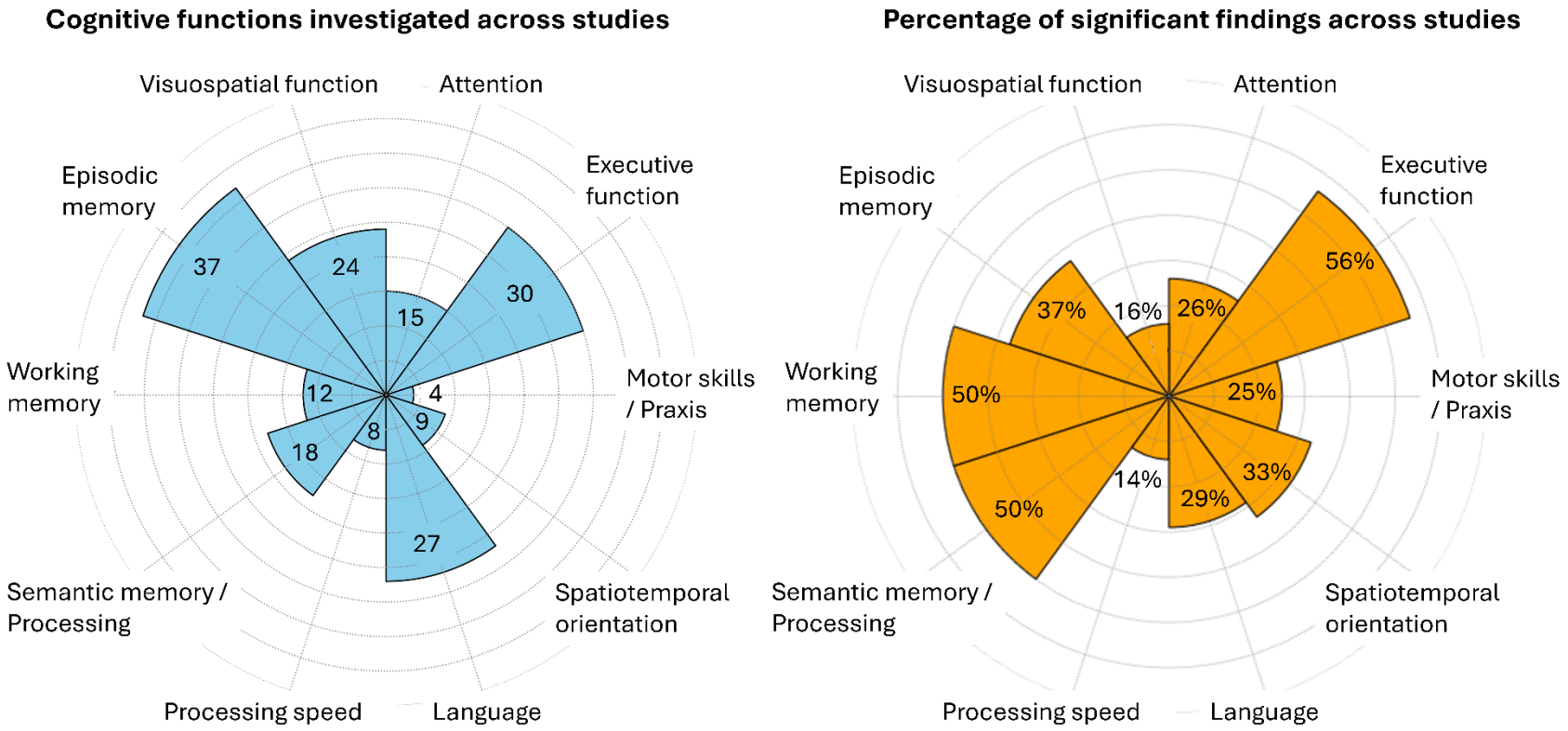
The majority of studies included batteries of tests and/or rating scales (at times in full, at times only subtests were employed) and performed their analyses to test the associations the associations between different manifestations of psychotic phenomena and several cognitive functions; only three studies specifically focused on one function (namely decision-making, executive function and attention). In twenty-

three studies, it was clearly indicated in their methods which tests were used as a measure of a specific cognitive function, in others this was normally inferred either based on other sections of the paper or (when not available) on the interpretation of cognitive functions related to specific assessment measures as described in the introduction of this thesis (and illustrated in Table 5.1).

Figure 5.2 provides a synthesis of the cognitive functions investigated overall (reporting the total number of studies that included them in their analyses), and the proportion of studies in which these were found significant. Table 5.1 provides deeper focus into the studies that investigated and found significant associations with different sub-domains and cognitive processes, as well as a synthesis of the assessment measures used (only those that are linked to significant findings).

Figure 5.2

Number of studies which investigated cognitive domains, compared to proportion of studies which identified significant associations



Note. The case study, and comparison of misidentification vs paranoia analysis performed in only one study were not included in the holistic overview, which rather shows results of samples of people with vs without psychotic symptoms.

Table 5.1

Cognitive functions investigated and studies in which these were found significant

Domain	Subdomain	Studies (numbered in order)	tot	Significant studies (numbered in order)	tot sig.	Tests used in significant studies
Visuospatial function		7,17,24,30,32,33,34,35,39,43	24	33	4	Rey Osterrieth Complex Figure (Copy), Developmental Test of Visual-Motor Integration
	Perception/object recognition	1,3,18,27,36		3,36		CAMCOG, Visual Object and Space Perception Battery
	Construction (copying/drawing)	6,9,10,19,23,26,27,28,29,30,36,42		30		K-CERAD (Constructional Praxis)
Motor skills/praxis		1,3,27,32	4	32	1	Grooved Pegboard Test
Attention		1,3,9,14,15,19,24,25,26,27,28,29,35,36,43	15	14,25,35,36	4	Digit Symbol Substitution Test, TMT-A, Multiple Features Targets Cancellation, CANTAB (Rapid Visual Information Processing)
Short-term/working memory	(verbal and visual/spatial)	6,12,13,15,18,20,32,33,35,37,39,43	12	15,18,20,32,35,43	6	Digit Span Forward and Backward (4), WMS - Mental Control subtest (2)
Episodic memory		1,9,10,13,16,17,19,21,22,23,24,25,29,32	37	19,21,25,32	14	DRS (Memory) (2), MCB, AVLT
	Verbal	3,10,20,37,40,42		40		DRS (Memory)
	Nonverbal/visual	3,10,20,26,27,35,36,37,40,43		35,40,43		Rey Osterrieth Complex Figure (Recall) (2), DRS (Memory)
	Encoding (learning)	1,7,18,27,28,39		7,39		Hopkins Verbal Learning Test (2)

Domain	Subdomain	Studies (numbered in order)	tot	Significant studies (numbered in order)	tot sig.	Tests used in significant studies
	Recall/recognition	4,6,7,10,12,15,26,30,33,34,35,36,43		7,15,30,34,35		Hopkins Verbal Learning Test (Recognition), WMS-R (Logical Memory), Word List Recall (also ADAS-Cog and RAVLT)
	Source monitoring	13		13		Three Categories Source Monitoring Test
Semantic memory/processing		1,6,7,9,10,15,17,19,20,21,22,30,32,33,35,36, 39,42	18	7,10,15,19,30,32,33,35, 42	9	Semantic Fluency Test (4), DRS Semantic Fluency (1), K-CERAD Semantic Fluency (1)
Spatiotemporal orientation		1,3,4,6,21,22,29,34,40	9	4,22,40	3	MCB, Status Questionnaire, DRS (orientation in memory subscale)
Processing speed		7,15,16,20,24,32,37,43	8	7	1	TMT-A
Executive functioning		2,7,9,15,18,20,23,25,30,32,33,35,36,37,39	30	7,18,25,35	16	TMT-B (2), Behavioural Dyscontrol Scale, Wechsler Memory Scale-Mental Control subtest (2), Stroop Test
	Reasoning/ abstraction	1,3,9,17,19,27,37		1,3,19		CAMCOG (2), DRS (Conceptualisation)
	Updating	11				
	Similarities	8,29,31		31		FAB
	Patterns/sequencing	8,31		31		FAB
	Problem solving	8,19,26				
	Planning	41		41		ADAS-Cog 3 Mazes Completion Time
	Cognitive flexibility	10				

Domain	Subdomain	Studies (numbered in order)	tot	Significant studies (numbered in order)	tot sig.	Tests used in significant studies
	Inhibition/impulse resistance/ memory suppression	8,11,12,31,41		11,12,31		Stroop Test, FAB, Directed Forgetting Task
	Interference	31				
	Shifting/switching	8,11,16		8,16		WCST (Perseverative Errors, Total Switches)
	Concentration	4,41		41		Cancellation Task
	Insight/judgement	4,29,40				
	Decision-making	5		5		MacCAT-T
	Phonemic fluency	3,8,9,12,13,15,16,18,27,28,32,37,35		8,16,32,35		COWAT, Phonemic Fluency Test(3)
Language/verbal skills		6,26,33,42	27		8	
	Naming/ expressive	1,3,7,9,10,16,17,18,19,20,23,24,25,27, 28,29,30,32,34,35,36,37,43		1,10,23,25,34,35		CAMCOG, BNT (3), Object Naming (2)
	Receptive/ commands	1,3,16,24,27,29,34		1,24,27		CAMCOG, Token Test, Auditory Comprehension

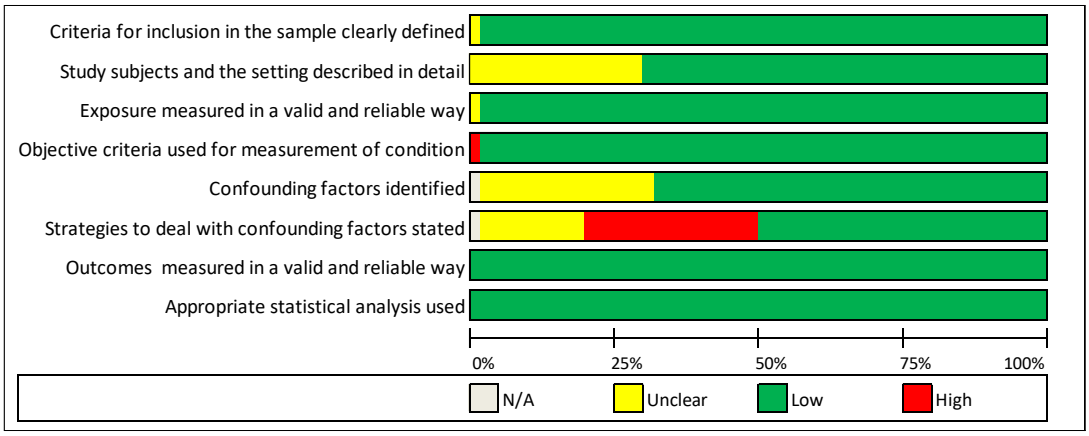
Notes. Study number is assigned based on the alphabetical order of the first author for each study, irrespective of symptom group. *Abbreviations*. CAMCOG = Cambridge Cognition Examination; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DRS = (Mattis) Dementia Rating Scale; TMT = Trail Making Test; WMS = Wechsler Memory Scale; CANTAB = Cambridge Neuropsychological Test Automated Battery; RAVLT = Rey Auditory Verbal Learning Test; MCB = Modified Confabulation Battery; FAB = Frontal Assessment Battery; WCST = Wisconsin Card Sorting Test; BNT = Boston Naming Test.

5.4.3. Quality appraisal and risk of bias assessment

Holistic appraisal of the study quality and risk of bias assessment is represented in Figure 5.3. Some of the items had very low risk of bias, namely those relating to the exposure measure (i.e., cognitive tests as predictors of psychosis classifications), the outcomes and choice of statistical analysis, which were clearly described in all studies, and the criteria for inclusion in the sample, and objective criteria for measurement of condition (psychotic symptoms), which were typically well defined with few exceptions. However, the study subjects were not always clearly described (i.e. the number of participants presenting with the symptoms of interest were not reported in almost a third of the studies and instead information on only the total number of subjects was included), thus presenting a moderate risk of bias; similarly, the two items relating to confounding factors had moderate to high risk: in about one fourth of the studies confounding factors were not clearly reported, and therefore no strategy was indicated in the study, and in a further one fourth of the studies, while identified, no clear strategy was indicated to account for those. This resulted in only half of the studies presenting low bias with respect to the item “strategies to deal with confounding factors stated”.

Figure 5.3

Visual depiction of the results of the JBI risk of bias assessment tool



Notes. Exposure is here defined as a factor that may be associated with the outcome of interest (i.e., the different manifestations of psychotic symptoms) (Lee and Pickard, 2013), therefore it consisted of the cognitive assessment.

5.4.4. Cognitive functions in relation to psychotic symptoms considered as a cluster

The studies that performed investigation on psychotic cluster (pooling together participants with delusions and hallucinations), are summarised in Figure 5.4 and Table 5.2.

Impaired executive function was found in relation to the presence as well as future manifestation of psychosis in most studies, specifically relating to processes such as mental control (Chen et al., 1998; Hopkins & Libon, 2005), inhibition and impulse resistance through the Stroop test (Quaranta et al., 2015) and the expanded ADAS-Cog mazes (Swanberg et al., 2004). Working memory was found to be associated with psychosis in two cross-sectional (Koppel et al., 2012; Quaranta et al., 2015) and one longitudinal (Paulsen, Ready, et al., 2000) study.

Paulsen et al. (2000), Quaranta et al. (2015) and Starr and Lonie (2007) also found impairment in episodic memory. Weamer et al. (2009) and Quaranta et al. (2015) found associations with psychotic symptoms and worse performance on the Rey-Osterrieth Complex Figure Recall (respectively delayed and immediate), indicative of impaired visual episodic memory.

Reeves et al. (2015) found an association between psychotic symptoms and the Visual Object and Space Perception Battery, a measure of visuospatial function (Warrington et al., 1991).

Worse performance on the semantic fluency test (Defrancesco et al., 2020; Tsai et al., 2010) as well as both semantic and phonemic (Paulsen, Ready, et al., 2000) was found in relation to future manifestations of psychotic symptoms.

Receptive language measured with the Token test, auditory comprehension and reading was found to be affected by Lopez et al. (1991), while lower score in the Boston Naming Test predictive of higher rates of psychosis at a two-year interval (Defrancesco et al., 2020).

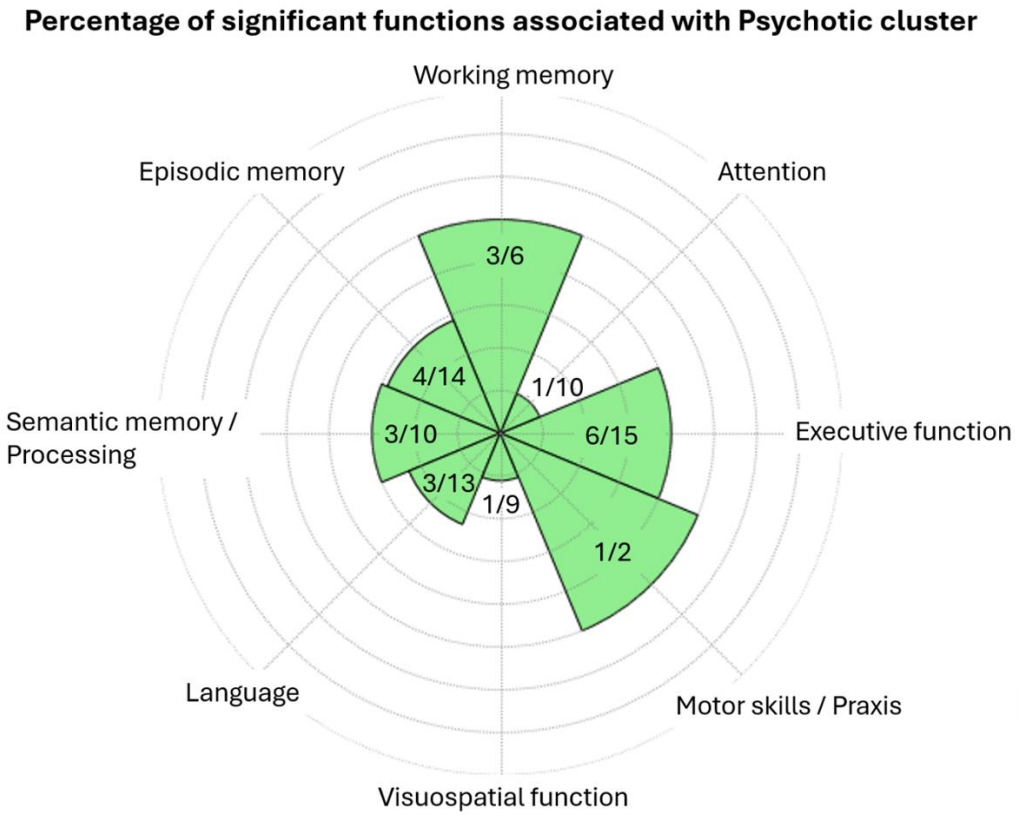
A more rapid rate of decline in a measure of attention was found by Emanuel et al. (2011), while Reeves et al. (2015) found worse performance in the rapid visual information processing of the Cambridge Neuropsychological Test Automated Battery (Fray et al., 1996).

Paulsen's longitudinal study (2000) identified an association with motor skills through the grooved pegboard test and future manifestations of psychotic symptoms.

Lastly, two studies investigated delusions and hallucinations alongside other neuropsychiatric symptoms (that they found to load within a psychotic cluster in previous factor analyses), namely aberrant motor behaviour (Aalten, Jolles, et al., 2007), and aberrant motor behaviour and agitation (Rouch et al., 2020). These respectively found greater impairment on language expression and abstract reasoning, and conversely less impaired executive function as shown from higher score on the mini-frontal assessment battery (FAB) (Dubois et al., 2000) in relation to the psychotic cluster.

Figure 5.4

Proportion of significant functions in relation to psychotic cluster



Notes. The figure represents the number of studies in which a cognitive function was significant, divided by the total number of studies in which that function was investigated.

Table 5.2

Studies on psychotic cluster

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Aalten et al., 2007 1	Psychosis* (including agitation)	100 AD patients, 15 with vascular dementia, 11 multiple aetiologies	longitudinal	hypothesized that specific types of cognitive impairment, (particularly language) are related to more severe psychotic symptoms	global dementia severity	1. episodic memory, 2. naming abilities, 3. semantic memory, 4. language (comprehension and expression), memory (recent, remote, and new learning), attention/ calculation, praxis, abstract reasoning, perception, and orientation	1. 10-Item Word List Memory Task Based On The Auditory Verbal Learning Test, 2. Aachen Aphasia Test, 3. Verbal Fluency Test, 4. CAMCOG	$p<0.05$	significant main effects of language and expression) and abstract reasoning on psychosis	Language, executive function
Chen et al., 1998 8	Psychosis	31 AD patients	cross-sectional	executive dysfunction is associated with greater neuropsychiatric symptomatology and functional impairment; relationships between executive dysfunction and specific types of neuropsychiatric symptoms	MMSE	executive function through seven aspects: 1. verbal fluency, initiation, 2. similarities, abstraction, 3. verbal and motor sequences, patterns, initiation, 4. response inhibition, 5. divided attention, sequencing, 6. problem solving, 7. set shifting and flexibility	1. Controlled Oral Word Association Test FAS Subtest, 2. Mattis Dementia Rating Scale (DRS), 3. MDRS Initiation, 4. Stroop Interference, 5. Trail Making Part B, 6. Wisconsin Card Sorting Test, 7. WCST Perseverative Errors	$p<0.05$	significant relationship between poor executive functioning scores (in FAST subtest and WCST categories) and psychosis, before covarying with MMSE	Executive function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
D'Antonio et al., 2019 9	Psychosis*	32 AD patients, 17 with psychosis (6 paranoid subtype, 2 misidentification subtype, and 9 both) and 15 without	longitudinal	detecting whether impairment in specific cognitive domains predicts the onset of psychosis	not specified	1. memory 2. attention, 3. language, 4. visuo-constructional skills, 5. executive functions, 6. abstract reasoning ability	1. Rey's Auditory Verbal Learning Test, Corsi Block-Tapping Test, Digit Span, Babcock Story, 2. Visual Search Test, Trail-Making Test, 3. Boston Naming Test, 4. Clock Drawing Test, Rey-Osterrieth Complex Figure Test; 5. Semantic And Phonemic Verbal Fluency Test And Frontal Assessment Battery, 6. Raven's Progressive Coloured Matrices	Bonferroni's correction for multiple comparisons, $p<.004$	no significant findings	NA
Defrancesco et al., 2020 10	Psychosis	662 AD patients at baseline, 418 at first follow-up, 282 at second follow-up	longitudinal	investigate the influence of specific neuropsychiatric subsyndromes with cognitive decline of patients over time	MMSE, age, education	1. verbal memory and recognition, 2. constructional praxis, 3. figural memory 4. confrontational object naming, 5. verbal fluency, 6. cognitive flexibility	CERAD Battery: 1 Word List Learning, Word List Delayed Recall, And Word List Recognition, 2. Figure Drawing, 3. Delayed Recall, 4. BNT (Short Version), 5. Animals/Min, S-Words/Min, 6. Trail Making Test A And B	$p<0.05$ and $p<0.01$	at 2 years, higher rates of psychosis associated with lower Z score in verbal fluency animals and BNT	Semantic memory, language
Emanuel et al., 2011 14	Psychosis	350 with AD, mixed AD with vascular dementia or MCI (71 with psychosis, 279 without)	longitudinal	examine whether cognitive function in pre-clinical and early disease differs between AD with psychosis and AD without psychosis	age at baseline, race, gender, education, APOE4 grouping and psychotic grouping	1. attention	1. Digit Symbol Substitution Test	$p<.0003$	the "ever psychotic" group had a more rapid rate of digital symbol substitution test score decline	Attention
Hopkins and Libon, 2005 18	Psychosis	13 AD patients with psychosis, 14 without	cross-sectional	test the hypothesis that psychotic symptoms in patients with dementia might be due to relatively greater executive control and visuoperceptual deficits	no significant differences with controls on age, education, MMSE and Geriatric Depression Scale	1. executive control, 2. language/ semantic functioning, 3. visuoperceptual functioning, 4. memory and learning	1. Boston Revision Of The Wechsler Memory Scale-Mental Control Subtest, FAS Test Of Word List Generation, Clock Drawing, 2. Boston Naming Test (BNT), Animal Word List Generation Task, 3. Perceptual And Whole/Part Errors From The BNT 4. 9-Word Version Of The California Verbal Learning Test	$p<.05$, $p<.005$, $p<.001$	patients with psychosis obtained low scores on the Boston Revision Wechsler Memory Scale-Mental Control subtest	Executive function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Koppel et al., 2012 20	Psychosis	50 AD and 26 MCI patients	cross-sectional	determine correlations between behaviour and cognition (using a more sensitive psychometric instrument which might capture relationships which were previously gone undetected)	age, gender, functional impairment (CDR)	working memory, semantic memory, executive function, visual memory, verbal memory, language, processing speed (**)	Boston Naming Test, Benton Visual Retention Test, Consortium To Establish A Registry For AD Neuropsychology Assessment, Controlled Oral Word Test Phonemic Fluency And Animal/Vegetable/Fruit Semantic Fluency Task, Wechsler Memory Scale-Revised Logical Memory I And II, Digit Span, Wechsler Adult Intelligence Scale-Revised Digit Symbol Task, Clock Drawing Test	$p<.05$	psychosis was associated with working memory (digit span forward and backward) in the absence of an association with functional impairment	Working memory
Lopez et al., 1991 24	Psychosis	17 AD patients with psychotic symptoms (12 with delusions and 13 with hallucinations) and 17 without	longitudinal	evaluate the neuropsychological and neurophysiologic characteristics of AD patients in light of the presence of delusions and hallucinations	no significant differences with controls on age, gender, education, MMSE, duration of the symptoms	1. memory, 2. expressive language, 3. receptive language, 4. visuospatial, 5. speed/attention	1. Verbal And Face-Name Paired Associates, Immediate Recall Of A Figure And A Short Story, 2. Word Generation, Boston Naming Test, Writing; 3. Auditory Comprehension, Reading, Token Test-Part VI, 4. Visual Form Discrimination, Figure Copy, Three-Dimensional Block Design, 5. Letter Cancellation Time and Trail-Making Test (Part A)	$p<.001$	psychosis group performed worse on tests of receptive language than those without	Language
Makovac et al., 2016 26	Psychosis	58 AD patients	cross-sectional	correlations between regional GM atrophy and WM abnormalities of AD patients exhibiting psychotic symptoms, correlations *with cognitive functions were also performed*	not specified	1. verbal episodic long-term memory, 2. visuospatial episodic long-term memory, 3. short-term memory, 4. executive functions and attention, 5. language, 6. problem-solving, 7. praxis	1. Immediate And Delayed Recall Of A 15-Word List, Short Story Recall; 2. Delayed Recall Of Complex Rey's Figure; 3. Digit Span And Corsi Block Tapping Task; 4. Phonological Word Fluency; 5. Naming Subtest Of Aachener Aphasia Test; 6. Raven's Coloured Progressive Matrices; 7. Copy Of Drawings; Copy Of Complex Rey's Figure	Bonferroni's correction for multiple comparisons, $p<.003$	no significant findings	NA

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Paulsen et al., 2000 32	Psychosis	75 AD patients with psychosis at baseline, 60 at follow-up visit, 194 never psychotic	longitudinal	examine prognostic value of specific cognitive factors for psychotic symptoms of AD	age, education, gender, MMSE	episodic and working memory, attention, executive function, language, processing speed, verbal fluency, visuospatial function, motor skills (***)	Mattis DRS, WAIS-R Digit Span (Total Score), WISC – Revised Block Design, BNT, Verbal Fluency, WMS, Visual Reproduction Test, California Verbal Learning Test, TMT Part A And B, Grooved Pegboard Test, And The Modified Wisconsin Card Sorting Test	$p<.05$	baseline predictors: cumulative multivariate analysis revealed that the baseline measures of fluency, grooved pegboard test, and Digit Span (most robust) were predictors of future delusions or hallucinations; change in performance: in multivariate analysis were the fluency and total DRS scores	Praxis, working memory, episodic memory, semantic and phonemic (executive function) fluency (combined)
Quaranta et al., 2015 35	Psychosis*	48 AD patients with psychosis (42 delusions, of which 16 paranoia, 11 misidentification and 15 both; 23 hallucinations, of which 6 without delusions) and 60 without	cross-sectional	patients with paranoia should be less cognitively impaired; patients with misidentification and hallucinations should show severe impairment, particularly on executive function (misidentification) and visuospatial tasks (hallucinations)	age, educational level, illness duration, MMSE, and total score obtained on the other categories	episodic and working memory, attention, executive function, language, visuospatial function, semantic memory (**)	RAVLT, ROCF – Copy And Recall, RPM, Digit And Visuospatial Span, Immediate Visual Memory, Phonological Verbal Fluency, Semantic Verbal Fluency, Object Naming, Stroop's Test (Short), Copy Of Object (with and without Landmarks), MFTC	$p<.05$	mixed group performed worse than controls on RAVLT, immediate visual memory, digit span backward, and Stroop's test	Episodic (verbal and visual) and working memory, executive function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Reeves et al., 2015 36	Psychosis*	34 AD patients with psychosis, 36 without	cross-sectional	performance on tests of motor speed and sustained visual attention (correlated with striatal dopaminergic function) would differ between psychotic and nonpsychotic, and differences in performance would be largely accounted for by the paranoid subtype; establish neuropsychological profile of psychosis in AD	age, MMSE score and years of education; medication status included as fixed factors; no significant difference in education, illness duration, medication, and only trend for lower MMSE	1. motor speed and sustained visual attention, 2. executive function, 3. memory, 4. language, 5. constructional praxis, 6. visuoperceptual function	1. Cambridge Neuropsychological Test Automated Battery (Rapid Visual Information Processing , Motor Screening, Simple Reaction Time), 2. Digit Span, Semantic And Phonemic Fluency And Hayling Sentence Completion Task, 3., Immediate Verbal Recall, Delayed Verbal Recall and Recognition, Delayed Visual Recall and Recognition, 4. BNT, 5. The Clock Drawing Task and Shape Drawing Task, 6. Visual Object and Space Perception Battery (Incomplete Letters, Object Decision, Cube Analysis, Number Location)	Bonferroni's correction for multiple comparisons, $p<.05$	significant main effect of psychotic symptoms on the rapid visual information processing task	Visuospatial function
Rouch et al., 2020 37	Psychosis (including aberrant motor behaviour and agitation)	153 patients with prodromal AD and 84 mild AD	longitudinal	evaluating the link between baseline specific cognitive functioning and subsequent psychosis occurrence in participants with prodromal or mild AD	age, gender, educational level, MMSE	1. long-term verbal memory, 2. visual recognition memory, 3. speed processing and executive function, 4. speed and inhibition, 5. executive function, semantic memory, language, 6. executive function, 7. working and short-term memory, 8. abstraction, 9. language	1. Free And Cued Selective Reminding Test, 2. Delayed Matching-To-Sample, 3. Trail Making Test Part A And B, 4. Stroop, 5. Letter and Category Fluency, 6. Mini-Frontal Assessment Battery (FAB), 7. Digit Span Task, 8. Similarities Subtest of the Wechsler Adult Intelligence Scale, 9. 80-Item Object Naming Test	$p<.05$	higher score (indicative of better performance) on mini-FAB was significantly associated with higher psychotic symptoms	NA

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Starr and Lonie, 2007 39	Psychosis	556 AD patients	cross-sectional	describe relationships between psychotic symptoms and cognitive ability in patients with AD, and whether relationships were stronger for absolute cognitive status or for cognition relative to premorbid mental ability	not specified	1. verbal memory/learning new ability, 2. executive/frontal function, 3. visuospatial learning, visual and working memory	1. Hopkins Verbal Learning Test, 2. Category/Semantic Fluency, Lexical Verbal Fluency/Controlled Oral Word Association Test, 3. Paired Associate Learning, Delayed Matching To Sample	$p<.05$	psychotic factor correlated significantly with Hopkins Verbal Learning Test	Episodic memory
Swanberg et al., 2004 41	Psychosis	131 AD patients and 64 cognitively normal	longitudinal	hypothesized that patients with executive dysfunction would have more abnormal behaviours	no significant differences with controls on age, years of education, and duration of dementia	executive function, specifically 1. concentration and search strategies, 2. impulse resistance, planning, reasoning, foresight	1. Cancellation Tasks, 2. Time To Complete The First 3 Mazes From Expanded ADAS-Cog	Holm's adjustment for multiple comparisons, $p<.05$	3 maze time and cancellation task was significantly associated with frequency of psychosis at baseline and 12-month visits	Executive function
Tsai et al., 2010 42	Psychosis	101 AD patients, 33% delusions, 14% hallucinations at baseline	longitudinal	examine the patients with diagnosis of AD to determine whether baseline Mini-Mental State Examination (MMSE) or CVFT was related to the changes in behavioural disturbances at a follow-up study	time (in months) between initial and follow-up assessments, age, education, gender, and baseline NPI total score	1. semantic memory, executive function, language, 2. visuospatial and constructional abilities, 3. verbal memory	1. Category Verbal Fluency Test, 2. Constructional Praxis Test From CERAD, 3. Delayed Word Recall Test	$p<.01$	category verbal fluency test associated with, and predictive of, changes in psychosis subdomain	Semantic memory

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuropsychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Weamer et al., 2009 43	Psychosis	112 AD or MCI patients with psychosis and 239 without	longitudinal	determine what neuropsychological domains contributed to the association of global cognitive impairment with subsequent onset of psychosis	MMSE, age, education, age of onset, gender, Cognitive Enhancer (CE) use	immediate and delayed memory, attention, working memory and visuospatial and language abilities (**)	AD Assessment Scale, Rey-Osterrieth Complex Figure, Benton Visual Discrimination Test, Digit Span Forwards And Backwards Test, Phonological Fluency Test, Boston Naming Test, Trail Making Test	$p<.05$	reduced time of onset of psychosis associated with greater impairment on the Rey-Osterrieth Complex Figure Delayed Recall and better performance on Forward Digit Span	Episodic (visual) memory

Notes. When the study included separate analyses of other neuropsychiatric symptoms, this is indicated (*); when the cognitive functions are explicitly linked to a neuropsychological assessment in the study, this has been reflected in the columns cognitive function investigated and neuropsychological assessment by assigning corresponding numbers; for the other studies, the information was either present elsewhere in the article (**), or it was inferred by the reviewers (***). Only results relating to tests or sub-tests of specific cognitive functions are reported (i.e., results relating to global cognition, e.g., MMSE score, are not reported). *Abbreviations*. WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; DRS = (Mattis) Dementia Rating Scale; BNT = Boston Naming Test; TMT = Trail Making Test; RAVLT = Rey's Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; RPM = Raven's Progressive Coloured Matrices; MFTC = Multiple Features Targets Cancellation

5.4.5. Cognitive functions in relation to delusions

The studies that performed investigation on the associations of delusions are summarised in Figure 5.5 and Table 5.3.

Seven studies found impairments in different executive functions: Castelluccio et al. (2020) in the Behavioural Dyscontrol Scale (Grigsby, 1996) and the Trail Making Test – part B, the latter was also identified by Lü et al. (2021); Fischer et al. (2006) found impairment in the phonemic fluency, Fischer et al. (2012) found worse scores in the "switches" element of the Wisconsin Card Sorting Test, while using the Frontal assessment battery (Dubois et al., 2000), Nagata et al. (2009) found worse total score, as well as on the sub-scores of similarities, motor series, and conflicting instructions. Aalten, Jolles, et al. (2007) found an association with impaired abstract reasoning and delusions, while Bertrand et al. (2017) found that lower score on the expression scale of the MacArthur Competence Tool for Treatment (Grisso et al., 1997) (a tool to assess decision-making ability in the context of capacity) was associated with the presence of delusions.

Fischer et al. (2006) found an association between delusions and the mental control task of the WMS-R, a measure of working memory.

Six studies found impairments in episodic memory: in Castelluccio et al. (2020) in relation to the Hopkins Verbal Learning Test (Brandt, 1991), in Lü et al. (2021) with the Auditory Verbal Learning Test, and Fischer et al. (2006) based on the immediate and delayed memory for short stories task of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987). Two (Jeste et al., 1992; Sultzer et al., 2014) based on the Mattis Dementia Rating scale (Jurica et al., 1988), and in two studies on the associations between delusions and confabulations (Lee, Akanuma, et al., 2007; Lee, Meguro, et al., 2007), associations were found between episodic content of confabulations and delusions. Lee, Akanuma et al. (2007) and Sultzer et al. (2014) also reported impaired orientation.

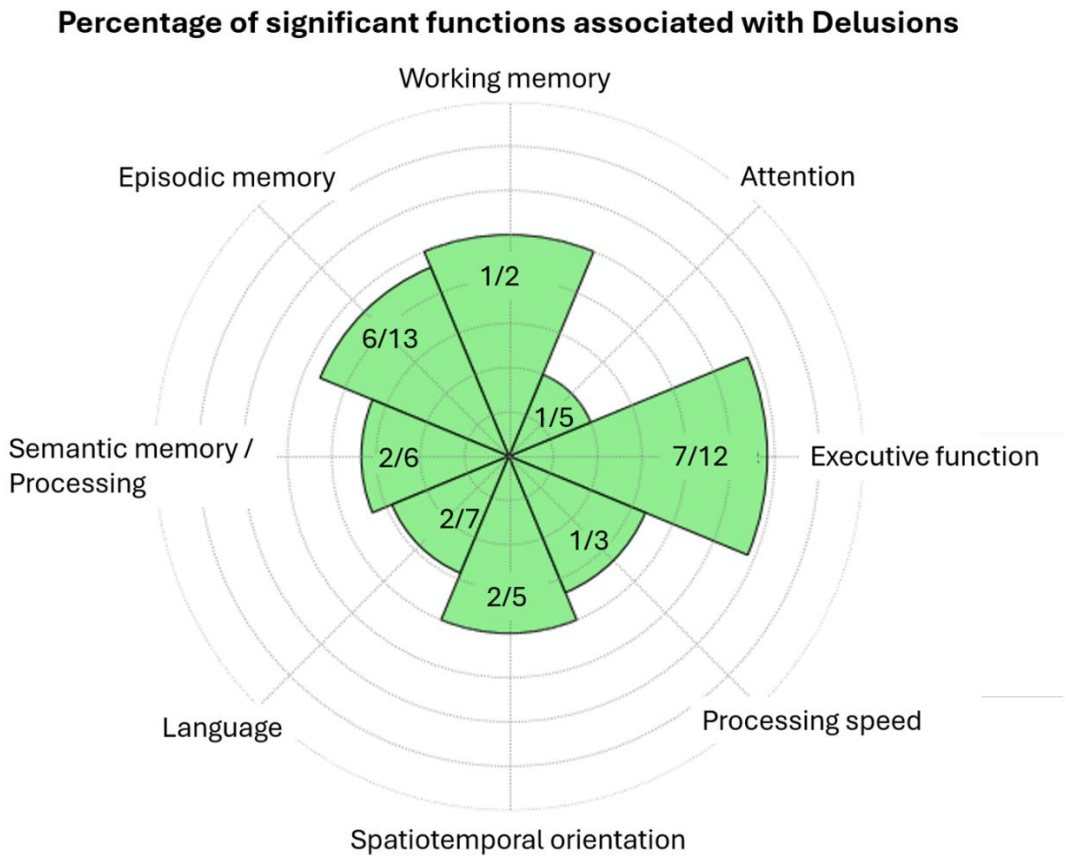
Semantic fluency tests were found to have lower scores in patients with delusions in two studies (Fischer et al., 2012; Jeste et al., 1992).

Migliorelli et al. (1995) found that severity of delusions correlated with a test for the verbal comprehension of commands, and Lü et al. (2021) in the Boston Naming Test.

Castelluccio et al. (2020) and Lü et al. (2021) found impairment in a measure of attention and processing speed, the Trail Making Test – part A.

Figure 5.5

Proportion of significant functions in relation to delusions



Notes. The figure represents the number of studies in which a cognitive function was significant, divided by the total number of studies in which that function was investigated.

Table 5.3

Studies on delusions

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Aalten et al., 2007 1	Delusions*	100 AD patients, 15 with vascular dementia, 11 multiple aetiologies	longitudinal	hypothesized that specific types of cognitive impairment, (particularly language) are related to more severe psychotic symptoms	global dementia severity	1. episodic memory, 2. naming abilities, 3. semantic memory, 4. language (comprehension and expression), memory (recent, remote, and new learning), attention/ calculation, praxis, abstract reasoning, perception, and orientation	1. 10-Item Word List Memory Task Based On The Auditory Verbal Learning Test, 2. Aachen Aphasia Test, 3. Verbal Fluency Test, 4. CAMCOG	$p<.05$	significant main effects of language and expression, and abstract reasoning (both from the CAMCOG) with delusions	Language, executive function
Back-Madruga et al., 2002 2	Delusions	20 AD patients (2 with delusions)	cross-sectional	investigate if subtype of AD patients with greater executive dysfunction (EAD) are associated with increased neuropsychiatric symptoms	not specified	1. executive function (including inhibition, verbal fluency, similarities)	1. Trail Making Test Part B, Stroop Test Part C, Controlled Oral Word Association Test Of Verbal Fluency, WAIS–R Similarities Subtest	$p<.05$	no significant findings	NA
Becker et al., 1994 4	Delusions*	49 AD and 15 multi-infarct dementia patients (87% with delusions and 48% with hallucinations)	cross-sectional	correlation between the incidence of psychopathology in dementia and the extent and quality of cognitive impairment	no significant differences with controls on gender	1. immediate, short-term and long-term memory, spatiotemporal orientation, concentration, judgement	1. Status Questionnaire	$p<.05$	no significant findings	NA
Bertrand et al., 2017 5	Delusions*	71 AD patients	cross-sectional	explore relationships between behavioural disturbances and decision making in AD by comparing those with or without BPSD	ADAS-Cog-11, gender education, age and dementia severity	1. decision-making	1. Macarthur Competence Tool For Treatment (comprising of: Understanding, Appreciation, Reasoning, Expression)	$p<.05$	patients with delusions had a lower score on the expression scale of the MacCAT-T	Executive function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Castelluccio et al., 2020 7	Delusions of theft, Othello (jealousy), misidentification, Capgras	185 patients with neuro cognitive disorders with delusions, 185 AD without	longitudinal	determine the cognitive severity and profile of delusion-positive patients with mild or major neurocognitive disorder, and to determine whether delusion type can be distinguished by cognitive features	demographic and clinical confounds through matching of control sample	executive function, verbal fluency, language, visuospatial and verbal memory, working memory, processing speed	Behavioural Dyscontrol Scale, Trail Making Test, Controlled Oral Word Association, Semantic (Animal) Fluency, Boston Naming Test, Beery Visuomotor Integration Test, Brief Visuospatial Memory Test Revised, Hopkins Verbal Learning Test Revised	Bonferroni's correction for multiple comparisons, $p<.05$	worse performance in delusion positive on BDS, and TMT A and B, and executive aspect of memory (HVLT-R) - only TMTB survived Bonferroni correction	Processing speed, executive function, episodic memory
El Haj et al., 2015 11	Delusions*	31 AD and 33 healthy older adults' controls	cross-sectional	hypothesised that inhibitory decline plays a major role in delusions and hallucinations in individuals with AD; inhibition would mediate the relationship between hallucinations–delusions and executive dysfunction or psychological distress	not specified	1. episodic memory, 2. inhibition, 3. shifting, 4. updating (2, 3 and 4 as processes relating to executive function)	1. 5-Words Test, 2 Stroop Task, 3. Plus–Minus Task, 4. 2-Back Task	Bonferroni's correction for multiple comparisons, $p<.05$	no significant findings	NA
Fischer et al., 2006 15	Delusions	9 AD patients with delusions and 9 without	cross-sectional	predicted that patients with delusions would perform more poorly than patients without delusions on most, but not all, neuropsychological measures	no significant differences with controls on age, education, gender, exclusion of people with hallucinations	1. processing/ psychomotor speed, 2. semantic and phonemic fluency, 3. immediate and delayed memory, 4. attention, 5. working memory, 6. executive function	1. Trail Making Test Part A, WAIS-R Digit Symbol, 2. Semantic Fluency, Phonemic Fluency tests, 3. WMS-R (Logical Memory, Visual Reproduction, Verbal Paired Associates, 4. WMS Digit Span, Visual Span 5. WMS Mental Control, 6. Trail Making Test Part B, WAIS-R Comprehension	$p<.05$	those with delusions performed poorer on WMS-R logical memory test, semantic fluency task and WMS-R mental control than those without	Episodic, semantic and working memory

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Fischer et al., 2012 16	Delusions	19 AD patients with delusions and 19 without	cross-sectional	hypothesised that AD patients would be more functionally impaired compared to non-delusional controls (and have greater behavioural symptoms and increased caregiver burden - all these differences would correlate neuropsychologically with frontal executive deficits)	no significant differences with controls on age, education and MMSE	memory, verbal fluency, processing speed, language and executive functions (**)	National Adult Reading Test, Word List Generation, Wisconsin Card Sorting Test, Trail Making Test Part A And B, Boston Naming Test, Token Test And California Verbal Learning Test	$p<.05$	AD patients with delusions had worst performance on phonemic fluency and total switches	Executive function
Flynn et al., 1991 17	Delusions*	13 AD patients with delusions and 6 without	cross-sectional	compare dementia patients with and without delusions to determine if this behaviour change correlated with other neuropsychological and behavioural features, and secondarily test other elements of the BEHAVE-AD (including hallucinations) in correlation with neuropsychological tests	age, education, neuro-psychological deficits, or neurological or extrapyramidal abnormalities	1. memory, 2. language, 3. verbal fluency, 4. visuospatial ability, 5. abstraction	1. Shopping List Test, 2. Boston Naming Test, 3. Word List Generation Task (category), 4. Developmental Test Of Visual-Motor Integration, 5. identities and oddities of DRS	Bonferroni's correction for multiple comparisons, $p<.05$	no significant findings	NA

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Jeste et al., 1992 19	Delusions	37 AD patients with delusions, 70 without	cross-sectional	compare the performance of delusional and non-delusional groups on battery of neuropsychological tests	age, education, duration of illness	1. attention, 2. memory, 3. language, 4. problem solving, abstract thinking and conceptualisation, 5. constructional ability	1. WAIS-R Digit Span Subtest, Attention Subtest DRS, 2. Memory Subtest Of DRS, 3. BNT, Abbreviated, Verbal Fluency Test, Number Information Test, 4. Conceptualization/ Initiation Subtests DRS, Verbal Fluency Test, 5. Block Design Subtest Of WISC-R, Clock Drawing Test, DRS Construction Subtest	$p<.05$	patients with delusions performed significantly worse on memory subtest of DRS and two putative tests of frontal function (conceptualization subtest of DRS and category subtest of the Verbal Fluency Test)	Episodic and semantic memory, executive function
Lee et al., 2007 A 21	Delusions	21 AD patients with delusions and 29 without, and 10 healthy elderly controls	cross-sectional	examine the relationship between confabulations and delusions	not specified	1. semantic and episodic confabulations, spatiotemporal orientation	1. Modified Confabulation Battery (MCB)	$p<.05$	delusional group of AD patients showed significantly more confabulations for episodic subjects than semantic	Episodic memory
Lee et al., 2007 B 22	Delusions	32 AD patients and 10 healthy elderly controls	cross-sectional	AD patients with psychiatric symptoms would show significantly more confabulatory responses, compared to patients without such symptoms; whether cognitive ability was associated with confabulation	not specified	1. semantic and episodic confabulations, spatiotemporal orientation	1. MCB	$p<.05$	delusion group showed significantly more confabulations on questions associated with remembering the past, and future planning	Episodic memory, spatiotemporal orientation
Lu et al., 2021 25	Delusions*	236 AD 222 MCI	cross-sectional	association of psychotic symptoms and cognitive domains	not specified	1. language, 2. memory, 3. attention, 4. executive function	1. Boston Naming Test, 2. AVLT, 3. TMT-A, 4. TMT-B	$p<.05$	delusions associated with worse performance in learning; correlations, language, attention and executive function (all tests)	Attention, executive function, language, episodic memory

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Migliorelli et al., 1995 27	Delusions	21 AD patients with delusions and 82 without	cross-sectional	determine the prevalence and type of delusions in AD, and examine the presence of significant neurological, neuropsychological and psychiatric correlates	age, education, MMSE, duration of illness	1. verbal learning and memory, 2. visual perception and nonverbal memory, 3. ideomotor and 4. constructional apraxia, 5. auditory attention,6. developing new concepts and shift sets, 7. visual, conceptual and visuomotor tracking, 8. semantic information, 9. naming pictured objects, 10. verbal comprehension of commands of increasing complexity, 11. visuospatial reasoning	1. Buschke Selective Reminding Test (Long-Term Retrieval (LTR) And The Delayed Recall Stores), 2. Benton Visual Retention Test 3. Apraxia Subtest Of The Western Aphasia Battery, 4. Block Design, 5. Digit Span, 6. Wisconsin Card Sorting Test, 7. Trail Making Test, 8. Controlled Oral Word Association Test, 9. Boston Naming Test,10. Token Test, 11. Raven's Progressive Matrices	p=.008	severity of delusions correlated with Token Test (verbal comprehension of commands of increasing complexity)	Language
Nagata et al., 2009 31	Delusions	19 AD patients with delusions, 29 without	cross-sectional	investigate the relation between the manifestation of delusional thoughts and frontal lobe dysfunction in patients with AD	age, education (years), duration of illness (months), MMSE	1. similarities (conceptualization); lexical fluency (mental flexibility); motor series (programming); conflicting instructions (sensitivity to interference); go–no go (inhibition control); and prehension behaviour (environmental autonomy)	1. Japanese FAB Version	p<.05	FAB total score, and subtest scores of Similarities, Motor series, and Conflicting instructions, were significantly lower in AD patients with delusional thoughts than in those without delusional thoughts	Executive function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Sultzer et al., 2014 40	Delusions	28 AD patients with delusions, 60 without	cross-sectional	examine the clinical associations among delusional thoughts, memory deficits and poor insight in mild to moderate AD	not specified	1. memory (comprising orientation, verbal recall, verbal and visual recognition), 2. insight	1. Mattis Dementia Rating Scale (DRS) - Memory Subscale, 2. Neurobehavioral Rating Scale	$p<.001$	participants with delusions had lower DRS memory subscale	Episodic (verbal and visual) memory, spatiotemporal orientation

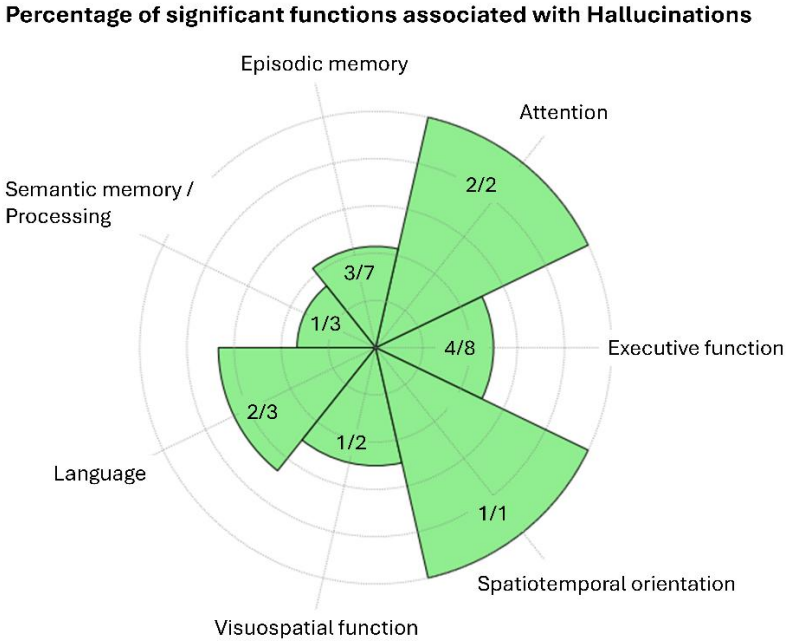
Notes. When the study included separate analyses of other neuropsychiatric symptoms, this is indicated (*); when the cognitive functions are explicitly linked to a neuropsychological assessment in the study, this has been reflected in the columns cognitive function investigated and neuropsychological assessment by assigning corresponding numbers; for the other studies, the information was either present elsewhere in the article (**), or it was inferred by the reviewers (***). Only results relating to tests or sub-tests of specific cognitive functions are reported (i.e., results relating to global cognition, e.g., MMSE score, are not reported). *Abbreviations*. WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; DRS = (Mattis) Dementia Rating Scale; BNT = Boston Naming Test; TMT = Trail Making Test; RAVLT = Rey's Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; RPM = Raven's Progressive Coloured Matrices; MFTC = Multiple Features Targets Cancellation

5.4.6. Cognitive functions in relation to hallucinations

The studies that performed investigation on the associations of hallucinations are summarised in Figure 5.6 and Table 5.4. Eight studies investigated cognitive functions in relation to hallucinations, only one of which longitudinal. The two studies by El Haj (2018; 2020) which focused solely on hallucinations, had a specific interest in processes relating to executive function and memory, and significant correlations were found, respectively, in suppressing memory representations, a process relating to executive function, and internal source monitoring, relating to episodic memory. Inhibitory performance was previously found to be more deteriorated by El Haj et al. (2015). Further correlations with measures of episodic memory were found in Lü et al. (2021) and Quaranta et al. (2015). Both Quaranta et al. (2015) and Lü et al. (2021) also found associations with measures of language, attention and executive function. Lastly, Becker et al. (1994) found associations with spatiotemporal orientation.

Figure 5.6

Proportion of significant functions in relation to hallucinations



Notes. The figure represents the number of studies in which a cognitive function was significant, divided by the total number of studies in which that function was investigated.

Table 5.4

Studies on hallucinations

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Correction	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Becker et al., 1994 4	Hallucinations *	49 AD and 15 multi-infarct dementia patients (87% with delusions and 48% with hallucinations)	cross-sectional	correlation between the incidence of psychopathology in dementia and the extent and quality of cognitive impairment	no significant differences with controls on gender	1. immediate, short-term and long-term memory, spatiotemporal orientation, concentration, judgement	1. Status Questionnaire (items)	$p<.05$	correlation between hallucinations and spatiotemporal orientation item of status questionnaire	Spatiotemporal orientation
Bertrand et al., 2017 5	Hallucinations *	71 AD patients	cross-sectional	explore relationships between behavioural disturbances and decision making in AD by comparing those with or without BPSD	ADAS-Cog-11, gender education, age and dementia severity	1. decision-making	1. Macarthur Competence Tool For Treatment (comprising of: Understanding, Appreciation, Reasoning, Expression)	$p<.05$	no significant findings	NA
El Haj et al., 2015 11	Hallucinations *	31 AD and 33 healthy older adults' controls	cross-sectional	hypothesised that inhibitory decline plays a major role in delusions and hallucinations in individuals with AD; inhibition would mediate the relationship between hallucinations–delusions and executive dysfunction or psychological distress	not specified	1. episodic memory, 2. inhibition, 3. shifting, 4. updating (2, 3 and 4 as processes relating to executive function)	1. 5-Words Test, 2 Stroop Task, 3. Plus–Minus Task, 4. 2-Back Task	Bonferroni's correction for multiple comparisons, $p<.05$	hallucinations were significantly correlated and predicted by inhibitory performances (Stroop test), which also mediates the impact of depression on hallucinations	Executive function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Correction	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
El Haj et al., 2018 12	Hallucinations	26 AD patients and 30 matched controls	cross-sectional	link between hallucinations and memory suppression in AD with the directed forgetting task (difficulty in suppressing words will be significantly correlated with the presence of hallucinations)	MMSE, depression, episodic memory (score on Grober and Buschke task)	1. working memory (phonological loop), 2. verbal episodic memory (immediate and delayed), 3. verbal fluency, 4. memory suppression	1. Digit Span Tasks (Forward And Backward), 2. Grober And Buschke, 3. P-Word Retrieval Task, 4. Directed Forgetting Task	$p<.05$	difficulties in suppressing memory representations with directed forgetting task were significantly correlated with the presence of hallucinations in the AD group	Executive function
El Haj et al., 2020 13	Hallucinations	25 AD patients and 27 matched healthy controls	cross-sectional	investigated the relationship between hallucinations in AD and difficulties in source monitoring (the ability to make judgements about the context in which information was acquired) and specific source monitoring category (reality, external or internal monitoring)	depression	1. episodic memory, 2. working memory, 3. verbal fluency, 4. source monitoring	1. Grober And Buschke Task (French), 2. Digit Span (Forward And Backward), 3. Verbal Fluency Test, 4. Three Categories Source Monitoring Test	Bonferroni's correction for multiple comparisons, $p<.012$	significant correlations between the presence of hallucinations and internal monitoring with three categories source monitoring test (but not reality or external monitoring) in AD	Episodic memory
Flynn et al., 1991 17	Hallucinations *	13 AD patients with delusions and 6 without, % with hallucinations not specified	cross-sectional	compare dementia patients with and without delusions to determine if this behaviour change correlated with other neuropsychological and behavioural features, and secondarily test other elements of the BEHAVE-AD *(including hallucinations)* in correlation with neuropsychological tests	age, education, neuro-psychological deficits, or neurological or extra-pyramidal abnormalities	1. memory, 2. language, 3. verbal fluency, 4. visuospatial ability, 5. abstraction	1. Shopping List Test, 2. BNT 3. Word List Generation Task (category), 4. Developmental Test Of Visual-Motor Integration, 5. identities and oddities of Mattis DRS	Bonferroni's correction for multiple comparisons, $p<.05$	no significant findings	NA
Lu et al., 25	Hallucinations *	236 AD 222 MCI	cross-sectional	association of psychotic symptoms and cognitive domains	not specified	1. language, 2. memory, 3. attention, 4. executive function	1. BNT, 2. AVLT, 3. TMT-A, 4. TMT-B	$p<.05$	hallucinations were significantly associated with worse performance in attention, executive function, language and episodic memory (all tests)	Attention, executive function, language, episodic memory

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Correction	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Quaranta et al., 2015 35	Hallucinations *	48 AD patients with psychosis (42 delusions, of which 16 paranoia, 11 misidentificati on and 15 both; 23 hallucinations, of which 6 without delusions) and 60 without	cross-sectional	patients with paranoia should be less cognitively impaired; patients with misidentification and hallucinations should show severe impairment, particularly on executive function (misidentification) and visuospatial tasks (hallucinations)	age, educational level, illness duration, MMSE, and total score obtained on the other categories	episodic and working memory, attention, executive function, language, visuospatial function, verbal fluency (**)	RAVLT, ROCF – Copy And Recall, RPM, Digit And Visuospatial Span, Immediate Visual Memory, Phonological Verbal Fluency, Semantic Verbal Fluency, Object Naming, Stroop's Test (Short), Copy Of Object (with and without Landmarks), MFTC	$p<.05$	participants with hallucinations performed worse on several cognitive measures i.e. RAVLT, ROCF delayed recall, RPM, immediate visual memory, phonological and semantic verbal fluency, object naming, MFTC accuracy and false alarms, and Stroop's test	Episodic memory, executive function, visuospatial function, semantic memory, language, attention

Notes. When the study included separate analyses of other neuropsychiatric symptoms, this is indicated (*); when the cognitive functions are explicitly linked to a neuropsychological assessment in the study, this has been reflected in the columns cognitive function investigated and neuropsychological assessment by assigning corresponding numbers; for the other studies, the information was either present elsewhere in the article (**), or it was inferred by the reviewers (***). Only results relating to tests or sub-tests of specific cognitive functions are reported (i.e., results relating to global cognition, e.g., MMSE score, are not reported). *Abbreviations*. WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; DRS = (Mattis) Dementia Rating Scale; BNT = Boston Naming Test; TMT = Trail Making Test; RAVLT = Rey's Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; RPM = Raven's Progressive Coloured Matrices; MFTC = Multiple Features Targets Cancellation.

5.4.7. Thematic subtypes: misidentification and paranoia

The studies that performed investigation on the associations of the thematic subtypes are summarised in Figure 5.7 and 5.8, and Table 5.5. Twelve studies performed analyses considering the thematic subtypes of psychotic symptoms in different ways: seven studies included analyses on both misidentification and paranoia (one of which separated delusions of misidentification from hallucinations); three had a specific focus on paranoid delusions (two of which only theft), while two (including the case study) focused on misidentification phenomena and Capgras syndrome.

Four studies in total reported results with regard to delusions of theft; two of them (Castelluccio et al., 2020; Na et al., 2018) found impairments in memory tasks such as word list recognition and recall (in association with both presence and severity of delusions) respectively. Na et al. (2018) also found associations with lower verbal fluency score and constructional praxis. Interestingly, Murayama et al. (2009) found that less impairment on the "speech sample", a subtest of the COGNISTAT in which the participant is asked to describe a scene shown in a drawing (Matsunaga et al., 2019), was found in the AD patients with delusions of theft, while Bylsma et al. (1994) found relatively preserved attention in relation to delusions of theft and abandonment.

Castelluccio et al. (2020) found verbal generativity to be more impaired in the participants with delusion of harm, while no correlations were found for delusions of jealousy or misidentification in this study. Lee et al. (2016) found lower scores on the Boston Naming test in relation to the presence of paranoid delusions (and none for misidentification).

In a study by Pontón et al. (1995), where most participants presented with Capgras delusions, lower scores were found on word recall and the object naming.

The case study (Shanks & Venneri, 2002) focused on three AD patients with misidentification: the main areas found to be impaired were long-term memory, abstract reasoning, executive functions and both visuoperceptual and visuoconstructional functions.

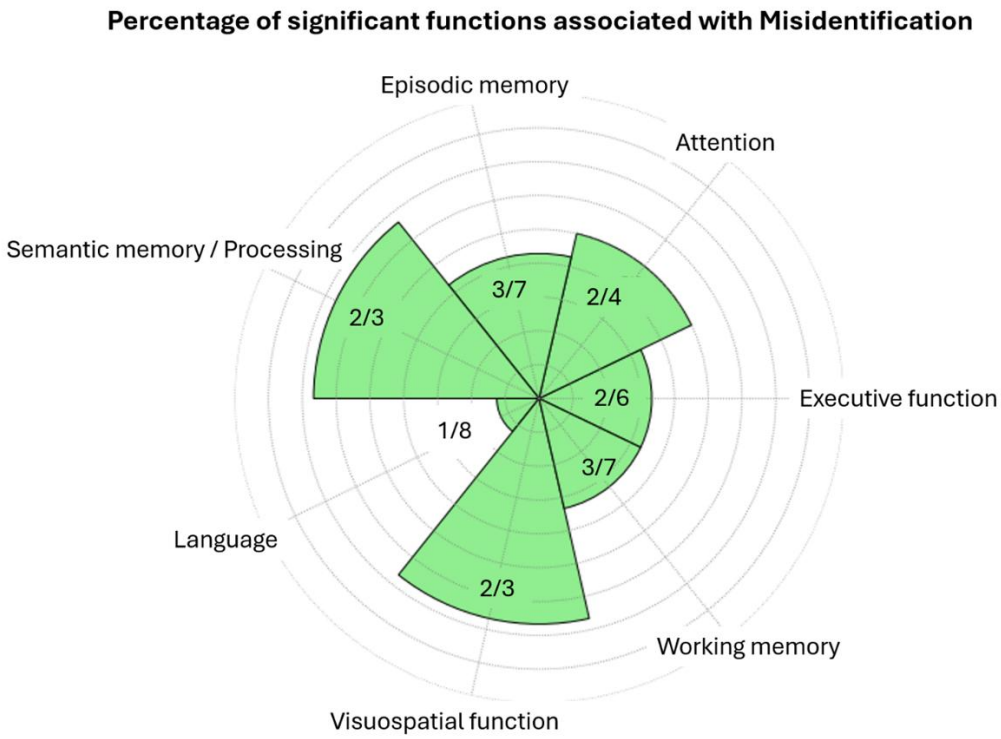
The misidentification subtype had worse performance compared to non-psychotic AD patients in the Rey Osterrieth Complex Figure copy and immediate recall (Perez-Madriñan et al., 2004; Quaranta et al., 2015), perception (Ballard et al., 1995) and visual

search (Quaranta et al., 2015), as well as verbal fluency (Perez-Madriñan et al., 2004; Quaranta et al., 2015), immediate (Perez-Madriñan et al., 2004) and delayed (Quaranta et al., 2015) episodic memory recall, abstract thinking (Ballard et al., 1995), Stroop's test (Quaranta et al., 2015) and performance in the rapid visual information processing and visuoperceptual tasks (Reeves et al., 2015).

Only Quaranta et al. (2015) directly compared paranoid and misidentification delusional subgroups, finding worse performance for the misidentification group in measures of episodic and working memory, Raven's Progressive Coloured Matrices (Raven, 2000) and verbal fluency.

Figure 5.7

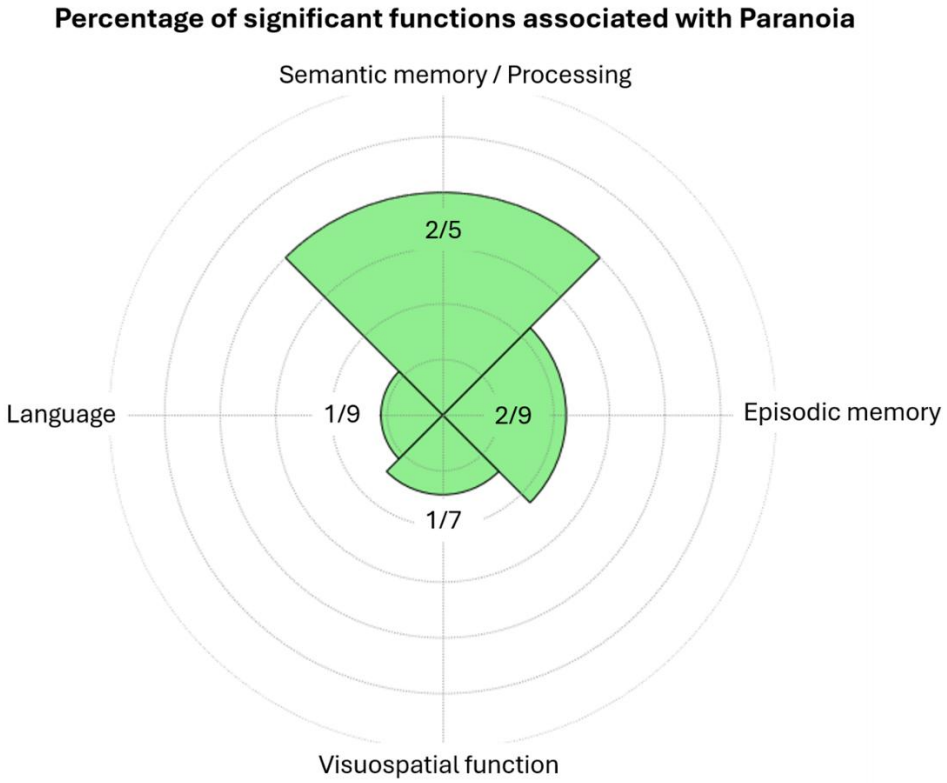
Proportion of significant functions in relation to misidentification



Notes. The figure represents the number of studies in which a cognitive function was significant, divided by the total number of studies in which that function was investigated.

Figure 5.8

Proportion of significant functions in relation to paranoia



Notes. The figure represents the number of studies in which a cognitive function was significant, divided by the total number of studies in which that function was investigated.

Table 5.5

Studies on thematic subtypes

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Ballard et al., 1995 3	Paranoia and misidentification	83 dementia patients with psychosis	cross-sectional	examining aetiology of delusions, visual hallucinations and delusional misidentifications (looking at characteristics of factors generated from principal component analysis)	not specified	orientation, language comprehension, language expression, praxis, recent memory, visual memory, remote memory, attention and calculation, perception, abstract thinking, verbal fluency	CAMCOG	$p<.05$	factor 1 (phantom-boarder delusions, visual hallucinations of animal and insects and visual hallucinations of strangers) was significantly associated with a lower score on perception; factor 3 (auditory hallucinations of strangers, delusional misidentification of television images and delusional misidentification of mirror images) was associated with lower scores for abstract thinking factor 2 (delusions of abandonment, persecutory delusions and delusions of reference) and 4 (visual hallucinations of relatives and delusions of relatives in the house) no associations	Executive function, visuospatial function
Bylsma et al., 1994 6	Delusions of theft, abandonment, somatic, "other"	45 AD patients with delusions, 135 without	cross-sectional	cognitive correlates of delusions in AD patients	no differences with controls on age, age of onset, duration of disease, gender, marital status, extrapyramidal motor signs, "familial" cases; excluded patients with hallucinations and misidentifications	orientation, registration, recall, short-term and working memory, attention/ calculation, semantic long-term memory, naming, language, construction	Modified MMSE (Subtests scores)	$p<.05$	deluded patients had relatively preserved attention and worse confrontation naming (not significant)	NA

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Castelluccio et al., 2020 7	Delusions of theft, Othello (jealousy), misidentification, Capgras	185 patients with neurocognitive disorders with delusions, 185 AD without	longitudinal	determine the cognitive severity and profile of delusion-positive patients with mild or major neurocognitive disorder, and to determine whether delusion type can be distinguished by cognitive features	demographic and clinical confounds through matching of control sample	executive function, verbal fluency, language, visuospatial and verbal memory, working memory, processing speed	Behavioural Dyscontrol Scale, Trail Making Test, Controlled Oral Word Association, Semantic (Animal) Fluency, Boston Naming Test, Beery Visuomotor Integration Test, Brief Visuospatial Memory Test Revised, Hopkins Verbal Learning Test Revised	Bonferroni's correction for multiple comparisons, $p<.05$	individuals with theft delusions performed worse on a core metric of memory storage (HVLT-R Recognition), and individuals with harm delusions performed worse on a measure of verbal generativity - neither survived Bonferroni correction	Episodic and semantic memory
Lee et al., 2016 23	Paranoia and misidentification	40 AD patients with psychosis, 25 without psychosis	cross-sectional	purpose of this study was to investigate the association between brain regional grey matter volume and the two subtypes of psychotic symptoms of paranoia and misidentification, *correlations with cognitive functions were also performed*	no significant differences with controls on age, gender, education and K-MMSE	1. memory, 2. language, 3. visuoconstructional praxis, 4. executive function	1.CERAD-K Word List Delayed Recall, 2. K-BNT, 3. CERAD-K Constructional Apraxia, 4. K-FAB	$p=.0008$	paranoid subtype had lower K-BNT scored compared to group without psychosis	language
Mizrahi et al., 2006 28	Paranoia, misidentification and expansive	155 AD patients with delusions of paranoia/ misidentification, 34 expansive, 58 mixed, 511 without delusions or hallucinations	cross-sectional	examine the frequency and clinical correlates of paranoid/misidentification and expansive delusions in AD	age and MMSE	1. Language, 2. Semantic information, 3. Verbal learning and Memory, 4. Auditory Attention, 5. Constructional Praxis	1. Boston Naming Test, 2. Controlled Oral Word Association Test, 3. Buschke Selective Reminding Test, 4. Digit Span, 5. Block Design	$p<.05$	no significant findings	NA

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Murayama et al., 2009 29	Delusion of theft	14 AD patients with delusions of theft, 42 without	cross-sectional	examined the risk factors for delusion of theft in AD patients showing mild dementia, focusing on social cognitive functions, cohabiting family members and premorbid personality traits	no significant differences with controls on mean age, years of education, MMSE and Hasegawa's dementia scale	1. orientation, attention, comprehension, repetition, naming, constructional ability, memory, calculation, similarities and judgement, 2. social cognitive function	1. COGNISTAT (11 Subtest Relating To Functions), 2. COGNISTAT Subtest "Speech Sample"	$p<.05$	significant differences on 'speech sample' subscale (not significant in logistic regression analysis with other predictors: gender, presence of cohabiting spouse and/or children, neurotic and extrovert personalities)	NA
Na et al., 2018 30	Delusion of theft	289 AD patients, 114 with paranoid delusions, 93 with delusions of theft, 82 without delusions	cross-sectional	determine the relationship between cognitive functions and delusion of theft in mild AD	not specified	language, memory, verbal fluency, executive function, visuospatial function (***)	K-CERAD: Verbal Fluency, 15-Item Boston Naming Test, Word List Memory, Word List Recall, Word List Recognition, Constructional Praxis, And Constructional Recall	$p<.05$	verbal fluency scores were significantly lower in paranoid delusions compared to delusions of theft and non-delusions; word list recall was significantly lower in delusions of theft compared to paranoid delusions and non-delusions (and did not differ between paranoid delusions and non-delusions); word list recall and constructional praxis correlated negatively with delusion severity in the delusion of theft group	Episodic and semantic memory, visuospatial function
Perez-Madrinan et al., 2004 33	Paranoia and misidentification	104 AD patients, 32 with misidentification, 24 with paranoia, 14 with both and 49 non-psychotic	cross-sectional	hypothesised that the paranoid and misidentification subtypes would differ in their patterns of cognitive impairment	age, education, duration of illness	immediate and delayed memory, visuospatial function, working memory, executive function, language (**)	ADAS 10-Item-Word-List Learning Test, 30 Minutes Recall Of Modified ROCF, Digit Span Forward And Backwards, Benton Visual Discrimination Test, Category Fluency Test	Bonferroni's correction for multiple comparisons, $p<.05$	misidentification group performed significantly worse than non-psychotic group on figure copy, figure copy immediate recall, verbal fluency (nonsignificant with MMSE as covariate)	Episodic (visual) and semantic memory, visuospatial function

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Pontón et al., 1995 34	Capgras syndrome	6 AD patients with delusions and 9 without	longitudinal	review the neuroimaging and cognitive progression of AD patients in whom psychosis developed over a 1-year interval	not specified	1. episodic memory, language, visuospatial abilities, orientation	1. ADAS-Cog	Bonferroni's correction for multiple comparisons, $p<.05$	delusional patients scored lower on word recall and object naming than non-delusional patients	Episodic memory, language
Quaranta et al., 2015 35	Paranoia and misidentification	48 AD patients with psychosis (42 delusions, of which 16 paranoia, 11 misidentification and 15 both; 23 hallucinations, of which 6 without delusions) and 60 without	cross-sectional	patients with paranoia should be less cognitively impaired; patients with misidentification and hallucinations should show severe impairment, particularly on executive function (misidentification) and visuospatial tasks (hallucinations)	age, educational level, illness duration, MMSE, and total score obtained on the other categories	episodic and working memory, attention, executive function, language, visuospatial function, verbal fluency (**)	RAVLT, ROCF – Copy And Recall, RPM, Digit And Visuospatial Span, Immediate Visual Memory, Phonological Verbal Fluency, Semantic Verbal Fluency, Object Naming, Stroop's Test (Short), Copy Of Object (with and without Landmarks), MFTC	$p<.05$	participants with paranoia performed better than controls at digit span forward; better than those with misidentification on RAVLT immediate recall and recognition accuracy, digit span backward, spatial span forward, RPM, phonological verbal fluency, and semantic verbal fluency; better than mixed group on RAVLT immediate recall and spatial span backward. misidentification participants performed worse than controls in RAVLT, ROCF delayed recall, RPM, semantic verbal fluency, phonological verbal fluency, MFTC accuracy, Stroop's test	Episodic, working and semantic memory, visuospatial function, executive function, attention

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Reeves et al., 2015 36	Paranoia and misidentification	34 AD patients with psychosis, 36 without	cross-sectional	performance on tests of motor speed and sustained visual attention (correlated with striatal dopaminergic function) would differ between psychotic and nonpsychotic, and differences in performance would be largely accounted for by the paranoid subtype; establish neuropsychological profile of psychosis in AD	age, MMSE score and years of education; medication status included as fixed factors; no significant difference in education, illness duration, medication, and only trend for lower MMSE	1. motor speed and sustained visual attention, 2. executive function, 3. memory, 4. language, 5. constructional praxis, 6. visuoperceptual function	1. Cambridge Neuropsychological Test Automated Battery (Rapid Visual Information Processing , Motor Screening, Simple Reaction Time), 2. Digit Span, Semantic And Phonemic Fluency And Hayling Sentence Completion Task, 3., Immediate Verbal Recall, Delayed Verbal Recall and Recognition, Delayed Visual Recall and Recognition, 4. BNT, 5. The Clock Drawing Task and Shape Drawing Task, 6. Visual Object and Space Perception Battery (Incomplete Letters, Object Decision, Cube Analysis, Number Location)	Bonferroni's correction for multiple comparisons, $p<.05$	poorer performance in the misidentification group compared to non-psychotic on rapid visual information processing task; lower sore in the misidentification group compared to nonpsychotic and paranoid on visuoperceptual performance (Visual Object and Space Perception Battery four components) and individual components follow-up only incomplete letters, with	Visuospatial function, attention

Author, Year	Symptom(s)	Participants	Design(s)	Aim(s) (in relation to this review)	Confounding Factors (accounted for in the analyses)	Cognitive Function(s) Investigated	Neuro-psychological Assessment	Statistical Threshold and Corrections	Relevant Findings (as reported in the study)	Relevant Findings (cognitive function)
Shanks and Venneri, 2002 38	Delusions of misidentification	3 AD patients with delusions	case studies	highlight association between deficits in visuospatial processing and misidentification in the context of a wider syndrome of right frontoparietal dysfunction	not applicable	attention, executive function, expressive and receptive language, visuoperceptual and visuoconstructional ability, short and long-term memory, abstract reasoning, fluency (**)	Raven's Progressive Matrices, Digit Cancellation, Stroop Test, Token Test, Confrontation Naming Test, Phonetic Fluency, Semantic Fluency, Graphic Fluency, Digit Span Forwards And Backwards, Paired Associates Learning, Visuoconstructive Apraxia Test	not applicable	PT1: mild long-term memory, nonverbal abstract reasoning task, and severe visuoperceptual and visuocostructive; PT2: mild long-term memory, severe abstract reasoning, fluency, visuoperceptual and visuocostructive deficits; PT3: severe abstract reasoning, moderate short- and long-term memory, severe executive dysfunction, object recognition, visuoperceptual and visuocostructive	Episodic memory, executive function, visuospatial function

Notes. When the study included separate analyses of other neuropsychiatric symptoms, this is indicated (*); when the cognitive functions are explicitly linked to a neuropsychological assessment in the study, this has been reflected in the columns cognitive function investigated and neuropsychological assessment by assigning corresponding numbers; for the other studies, the information was either present elsewhere in the article (**), or it was inferred by the reviewers (***). Only results relating to tests or sub-tests of specific cognitive functions are reported (i.e., results relating to global cognition, e.g., MMSE score, are not reported). *Abbreviations*. WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; DRS = (Mattis) Dementia Rating Scale; BNT = Boston Naming Test; TMT = Trail Making Test; RAVLT = Rey's Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; RPM = Raven's Progressive Coloured Matrices; MFTC = Multiple Features Targets Cancellation.

5.5. Discussion

In this chapter, a systematic review was conducted, to clarify the findings of the cognitive functions that were found in association with psychotic symptoms across the literature (up to January 2022). In fact, while it appears clear that the presence of psychosis in AD is associated with worse cognitive functioning at different disease stages (Ballard, 2024; Ismail et al., 2022), less clarity exists over which cognitive functions are more affected, particularly with regard to different manifestations of these symptoms.

The results derived have highlighted that specific cognitive functions and tests tend to relate to different manifestations of psychotic phenomena. The findings of this review partially confirm what has been identified in previous reviews, whereby deficits in executive functions were found in relation to delusions (Reeves et al., 2012), while working memory (Murray et al., 2014) and working memory and attention (Chatzikostopoulos et al., 2025) were identified in relation to psychosis as a cluster. However, within the present more comprehensive systematic review, further processes were highlighted, allowing for an interpretation of their contribution as underlying mechanisms, linking to the findings from a neuroanatomical perspective as discussed in chapter 3.

5.5.1. Executive functions and working memory

Investigated in most studies and showing a prominent ratio between investigations and significant findings were different processes of executive functioning, in relation to most psychotic phenomena (with the exception of paranoid delusions). Within this, working memory, which as seen above is considered a key executive process, was not extensively studied, however six out of twelve studies that included working memory tests (i.e., digit span and mental control subtest of the WMS), found these to be significantly more impaired in the participants presenting with psychotic cluster and delusions compared to controls (Fischer et al., 2006; Hopkins & Libon, 2005; Koppel et al., 2012; Paulsen, Ready, et al., 2000; Quaranta et al., 2015; Weamer et al., 2009), therefore warranting further investigation.

Other executive function's specific processes were more frequently investigated; while the interpretation attributed to each test slightly varied across studies (Table 5.1 shows

this), overall it appears that the most consistently impaired abilities relate to switching, as shown for example by worse functioning on the Trail Making Test – part B and the total number of switches performed on the Wisconsin Card Sorting Test (Chen et al., 1998; Fischer et al., 2012) and inhibition of automatic responses, assessed with the Stroop Test, or the inhibition subscale of the Frontal Assessment Battery, or in El Haj et al. (2018) as the impaired ability to intentionally forget, therefore a failure of inhibitory processes in relation to memory component. Furthermore, abilities related to decision-making (Bertrand et al., 2017), abstract thinking and reasoning (Aalten, Jolles, et al., 2007), planning (Swanberg et al., 2004), recognising patterns and similarities (Nagata et al., 2009), and phonemic fluency (Fischer et al., 2006; Quaranta et al., 2015) (which relies on processes such as controlled and effortful retrieval (Henry et al., 2004), updating and inhibition of incorrect responses (Shao et al., 2014)) were also highlighted, in relation to different manifestations of psychotic phenomena. Loss in overall executive functioning, including working memory, is associated with pathology within the prefrontal cortex (Uysal, 2023) as well as temporo-parietal areas (Daigle Katrina et al., 2022; Ossenkoppele et al., 2015): it would appear that the presence of psychosis, associated with greater atrophy in these areas, as seen in chapters 3 and 4, might manifest in concomitance with executive abilities, consistent with the notion that impairments in this domain tend to present globally across most processes (Lezak et al., 2012).

5.5.2. Semantic memory

While semantic memory was not as extensively explored as other functions such as executive function or episodic memory, from the ratio of significant findings against investigations, semantic memory, primarily measured using the semantic fluency test appears extremely relevant when it comes to discriminating all types of psychotic symptoms.

While both phonemic (mentioned above) and semantic fluency tests have been linked to Alzheimer's dementia (Olmos-Villaseñor et al., 2023), the semantic one appears to be consistently more impaired (Wright et al., 2023); the findings of this review suggest that within the Alzheimer's population, the presence of psychosis is linked to an even greater level of difficulty in this type of task, importantly also preceding symptoms manifestation (Castelluccio et al., 2020; Defrancesco et al., 2020; Tsai et al., 2010). While both semantic and phonemic fluency test rely on general lexical knowledge (Shao

et al., 2014) and executive processes, as seen in the previous section, semantic fluency places greater demand on semantic memory and processing, in addition to the abilities of clustering (generating words within a sub-category) and switching (change to a new sub-category) (Wright et al., 2023).

Semantic memory has recently been proposed as a potential marker of early AD pathology, detectable in advance of other clinical symptoms, as seen in chapter 1; in fact, impairment in this function appear to manifest even earlier than episodic memory (Loewenstein et al., 2017; Venneri et al., 2011; Venneri et al., 2008), consistently with atrophy in medio-temporal regions, inclusive of entorhinal cortex and perirhinal cortex, which is typical of initial stages of disease (Venneri et al., 2019). Greater atrophy in these regions has indeed been found in AD patients with psychosis compared to AD patients without psychosis, as it has been discussed in chapter 3. These findings seem to suggest that semantic memory as assessed with the semantic fluency test might not only be a good indicator of AD, but also of a psychosis phenotype within AD.

5.5.3. The role of episodic memory and spatiotemporal orientation

As expected, based on the literature (Harrison, 2022), measures of episodic memory were almost ubiquitously present in the studies selected. However, only roughly one third found significant correlations. Specifically, impaired encoding and recall/recognition were found mostly in relation to delusions, and in two out of the three studies on delusions of theft (Castelluccio et al., 2020; Na et al., 2018): it has been suggested that the failure to assimilate the correct information and to consider alternative possibilities (Sultzer et al., 2014), could be linked to the maintenance of rigidly held beliefs over time (Ting et al., 2015), which might contribute to explaining the presence of delusions, particularly relating to paranoia but also misidentification (as seen, for example, in Pontón et al., 1995) from a neuropsychological perspective. This could be linked to greater atrophy compared to non-psychotic patients in temporal areas: as described in chapter 3, particularly the parahippocampus was among the most frequently identified regions in relation to delusions, and the entorhinal cortex, specifically found in relation to misidentification, as seen in chapters 3 and 4. The parahippocampus is responsible for memory encoding and retrieval (Yoo et al., 2012), particularly in relation to contextual associative appraisal and processing (Aminoff et al., 2013; Prasad, 2019); the entorhinal cortex, on the other hand is involved in the

perceptual processing of stimuli, in novelty detection, associative learning, processing episodic recognition, and autobiographical memory (Prasad et al., 2004).

With regard to hallucinations, El Haj (2020) interestingly found associations with the impaired the ability to distinguish enacted from imagined happenings (internal source monitoring), which is a components of episodic memory. Two further studies (Lü et al., 2021; Quaranta et al., 2015) identified impaired performance in the Rey Auditory Verbal Learning test, indicating that episodic memory might be involved in hallucinatory process as well, although the paucity of studies on hallucinations warrants further investigation.

Visual memory, measured by tests which require the recall of a figure previously copied, as described in the introduction, was found significantly associated with psychotic cluster, delusions and hallucinations in one study per group (Quaranta et al., 2015; Sultzer et al., 2014; Weamer et al., 2009); impaired performance on tests of visual memory have been previously linked to temporo-occipital areas (Han et al., 2015; Mock et al., 2023). As this has not been as extensively studied as verbal episodic memory, its role in the manifestation of different psychotic phenomena could be further clarified.

Lastly, the role of orientation has not been extensively studied, however it resulted in significant associations in three out of nine studies, (two in relation to delusions, one of which specifically reporting greater impairment in delusional patients in episodic confabulations in relation to spatial and temporal orientation, and one to hallucinations). Interest is starting to be placed on this function in recent years, suggesting different presentation along disease continuum conceptualised as early spatiotemporal disorientation, followed by late social disorientation (Peters-Founshtein et al., 2023); spatial disorientation has also been linked to overall visuospatial functioning (Gerb et al., 2024), both found at earliest stages of disease. As a link with psychotic symptoms is suggested by these findings, and in relation to visuospatial function as detailed below, further investigation would be interesting, particularly relating to whether the element of social disorientation is more consistently impaired in people with psychotic symptoms.

5.5.4. Processing speed and attention

The study of these two functions was more complex compared to others such as episodic memory and executive function. In fact, fewer numbers of studies compared to the previously illustrated functions specifically focused on these aspects, with tests such as the Digit Cancellation and Digit Symbol Substitution Tests, the Multiple Features Targets Cancellation, and part A of the Trail Making Test, and associations were found particularly with hallucinations and misidentification; however, attention and processing speed are actually at the basis of the performance normally used to assess other functions as well, typically indicative of overall cognitive performance (Harvey, 2019; Lezak et al., 2012). Processing speed specifically has been found to be particularly impaired and an indicator of psychosis in other disorders such as schizophrenia (Dickinson et al., 2007; Knowles et al., 2010); on the other hand, both attention and processing speed tend to show greater impairment at more advanced disease stages (Haran et al., 2025; McGuinness et al., 2010): it would be interesting to clarify the role that these function have in psychotic symptoms in AD, with a study on stratified samples of participants.

5.5.5. Language

Language skills were found to be comparably impaired across all manifestations of psychosis, similarly to verbal fluency, albeit the proportion between studies and significant findings is much lower. Particularly in relation to the naming ability (therefore expressive language), a test of object naming, typically the Boston Naming Test was frequently included, however it was only significant in six out of the twenty-three studies; tests of comprehension were less common, and significant in three out of seven studies. Reflective of hippocampal damage, worse performance on the Boston Naming Test is evident in participants with AD, particularly at later stages of disease (Lezak et al., 2012), and this is consistent with the fact that of all psychotic manifestations, language impairments were more frequently found in association with hallucinations, which are typically linked to greater disease severity compared to delusions.

5.5.6. Visuospatial and visuoconstructional function

A typical test of visuospatial function is the Rey Osterrieth Complex Figure, where the copy element taps more into visuospatial and visuoconstructional abilities (while the

recall element taps more into visual memory (Lezak et al., 2012) as seen above). Constructional abilities were also frequently assessed within batteries, while less explored was the element of visual perception. Overall, the misidentification subtype was particularly associated with this domain: in fact, Perez-Madriñan et al. (2004) found the figure copy to be significantly worse, while Reeves et al. (2015) and Ballard et al. (1995) found associations with the perception component. Interestingly, many studies that investigated hallucinations did not focus on this function; further exploration of this might be needed, considered the associations found with the misidentification subtype. The neuroanatomical systematic review had identified an association with this subtype and the posterior cingulate, prefrontal and orbitofrontal cortices were frequently identified, as well as the lingual gyrus of the occipital lobe, and impairments in the ventral visual stream, suggesting a relationship with misperception and misinterpretation of stimuli (D'Antonio et al., 2019), which appears to find correspondence in the study of cognitive functions as well.

5.5.7. Motor skills and praxis

While visuoconstructional abilities are at times referred to as praxis, here the interpretation was based on Lezak's (2012) distinction between the two functions, according to which "constructional praxis" refers to the ability to copy or construct drawings or objects (as seen in the above section), while "pure praxis" (or the deficit of praxis which is referred to as apraxia) consists of the ideational and ideomotor components of knowing how to produce a multistep action and executing a skilled movement. Therefore, only four studies focused specifically on these elements, among which only Paulsen et al. (2000) found a relation between impaired performance in the Grooved Pegboard Test found and the manifestation of psychotic symptoms. The findings were not sufficient to draw clear conclusions, therefore further investigations might be useful to clarify this potential relationship.

5.5.8. Limitations

One limitation to consider was that the findings of the studies were synthesised without controlling for their methodological differences, such as aspects relating to their sample size, matched controls, covariates included in the analyses, or reported means of correcting for multiple comparisons when investigating the role of several cognitive

measures (however details are reported in the Tables 5.2 to 5.5). Furthermore, similarly to what proposed in chapter 3, it is the author's belief that further customisation of the risk of bias assessment tool might improve the overall assessment of the methodological strengths and weaknesses of included studies, such as the mentioned correction for multiple comparisons, as well as the clarity in terms of sample composition (i.e., how many participants presented with delusions and hallucinations when considering the psychotic cluster, or how many participants presented with specific delusional subtypes when considering the thematic components).

5.6. Conclusions

The aim of this systematic review was to provide a comprehensive synthesis of all the cognitive functions that have been found in association with psychotic symptoms in Alzheimer's disease dementia and Mild Cognitive Impairment. The main element of novelty was constituted by the analysis of the proportion of studies reporting significant findings relative to the total number of studies that investigated each cognitive function, with the process repeated for each sub-group of psychotic classification. This allowed clearer conclusions to be drawn on the value of each function: in fact, while functions such as episodic memory and expressive language were extensively studied and only moderately significant, others, such as semantic memory were much less investigated but presented a much higher ratio of studies with significant results to the total number of studies examining these cognitive function. In line with recent work on semantic memory (Loewenstein et al., 2017; Venneri et al., 2019; Wright et al., 2023) it is here proposed that further investigations should look into the role of this function in further understanding and classifying a psychosis phenotype in AD. Furthermore, while executive function and semantic memory showed significance across all or most manifestations, other functions were only relevant with respect to specific classifications, an example of which was visuospatial function, frequently associated with misidentification but not greatly relevant to other psychotic symptoms. Following the work on a more detailed classification of psychotic symptoms (Fischer, 2020), the findings of this review suggest that different psychotic subtype present with distinct cognitive profiles.

Chapter 6 – Study 3: Different manifestations of psychotic phenomena associated with specific cognitive domains and functions

6.1. Overview

In Chapter 5, a systematic review was presented that had the aim of clarifying the cognitive functions that tend to be more affected in relation to different manifestations of psychotic symptoms. This highlighted that while some functions were found to be impaired across all manifestations of psychotic symptoms, others were more specifically linked to certain phenomena. Considered the degree of variability in terms of methodology applied by the studies, the review proposed a method to evidence the cognitive functions that, when investigated, did result in significant correlations: this was done by calculating the proportion of significant associations given the total number of times each cognitive function was investigated, thus providing a synthesis of the findings based on the ratio. This allowed reflection on the role of certain key functions, such as semantic memory and executive function, which presented with the highest ratio (and which were linked to most manifestations of psychotic symptoms). On the other hand, episodic memory, which was the most extensively studied cognitive function, was only significant in about one third of the studies overall, and it was mostly associated to delusions; similarly, language, which was frequently investigated, was significant in only about one fourth of the studies, and mostly in relation to hallucinations. The review also highlighted that the misidentification subtype of psychosis was overall more associated with cognitive dysfunction compared to paranoia, and it was particularly related to visuospatial function. It was also evident that few studies seemed to consider it relevant to describe their sample composition: while investigating psychosis as a cluster, the number of participants who presented with delusions and hallucinations was not always specified; similarly, when investigating one symptom it was not always clear what strategies were employed to control for the presence of the other, if any. Furthermore, while the majority of studies focused on investigating associations between psychotic symptoms and individual tests, or sub-tests of batteries, few focused on cognitive domains.

In line with objective 5 of this thesis, the aim of this chapter is to perform a set of analyses that overcome these previous shortcomings, by testing the associations of specific manifestations of psychotic symptoms, with clear strategies to control for the

presence of the others, with cognitive domains and specific functions. Data for this study was obtained from ADNI: the Neuropsychiatric Inventory was used to select the samples of participants with psychotic symptoms and their matched controls; the MMSE was used as a measure of disease progression; neuropsychological variables selected from ADNI neuropsychological battery, and the Alzheimer's Disease Assessment Scale (ADAS-Cog-13). Participants were grouped into different manifestations of psychotic phenomena: a first group was formed consisting of participants who presented with either delusions, hallucinations, or both (psychotic cluster); sub-groups were then formed comprising of participants who presented with delusions, hallucinations, misidentification, paranoia and delusion of theft. Controls were matched to each group based on disease stage, age, gender and education, while the MMSE was used as a covariate in the analyses. A confirmatory factor analysis was first performed on the independent neuropsychological variables, to create composite scores corresponding to the cognitive domains of episodic memory, attention/executive function, visuospatial function and language. Consequently, two main regression models were created: one in which the predictors were the composite scores corresponding to the four cognitive domains, and another in which the individual neuropsychological tests were used as independent predictors of psychotic symptoms. Both models were tested on the dependent variables of the presence or absence of different manifestations of psychotic symptoms as described above. This chapter ends by discussing the findings, reflecting on the cognitive domains and specific functions that underpin psychotic phenomena and specific themes.

6.2. Introduction

As seen in the previous chapter, the relation between cognition and psychotic symptoms in AD dementia and MCI is a complex one. While it appears evident that when present, psychotic symptoms are associated with greater cognitive impairment starting from earlier stages of disease (Almeida et al., 2024; Connors, Ames, et al., 2018; Fuller et al., 2019), less clarity exists over the cognitive functions that, when dysfunctional, are associated with different types of psychotic phenomena. While a discrete body of literature has focused on addressing this issue, the results were overall only partially consistent across the studies, likely due to differences in their methodological approach

to statistical procedures, as well as neuropsychological variables and neuropsychiatric profiles of the participants.

Despite this, with a systematic approach to synthesis it was possible to identify some functions which tended to associate with most psychotic phenomena, and others specific to the different symptom presentations. For example, episodic memory, was mostly found in relation to delusions (this was also the case in those studies that specifically focused on paranoia or theft delusions), and it was involved in certain processes of hallucinations such as the generation of “false memories”, as defined in chapter 1. Visuospatial function was mostly found in association with misidentification. In addition, functions such as semantic memory and executive functions were significantly associated with most psychotic symptoms, leaving the question partially open as to whether it is possible to establish clear associations. Differences also emerged in terms of the symptoms groups: for example, while misidentification phenomena, when investigated, were almost ubiquitously associated with cognitive impairment, paranoid delusions were seldom linked to any cognitive dysfunction (e.g. Quaranta et al., 2015).

Considering the classification of psychotic symptoms, as was seen in both reviews (chapters 3 and 5), the majority of the studies grouped participants on the basis of them presenting either psychotic cluster or delusions, with fewer studies grouping participants based on their presentation of symptoms of hallucinations, and the themes of misidentification and paranoia. Furthermore, the complete neuropsychiatric profile was also not always available, therefore in the cluster studies the composition of the sample with respect to specific symptoms was explicit in only a portion of the studies; similarly, while a few studies on delusions (e.g. Castelluccio et al., 2020) reported the delusional subtypes present in their sample, the majority did not include this information, as this study intends to provide.

With regard to the variability of neuropsychological assessment, as well as statistical approach employed, while the majority of studies tested the associations using neuropsychological batteries, with different degrees of control for confounding factors and multiple comparisons, others (e.g. Back-Madruga et al., 2002; D'Antonio et al., 2019; Nagata et al., 2009) focused on one or a few cognitive domains. Within the current analyses, both approaches are explored and the findings compared.

In relation to this, one important point of reflection pertains to the methodology used for variable selection. While some studies provided information on whether a data-driven or other type of approach was used (e.g. Koppel et al., 2012, who reported using stepwise regression; Lopez et al., 1991, who used composite scores reflective of cognitive domains; Quaranta et al., 2015, in which both results deriving from univariable and multivariable analyses were provided), the majority did not specify this information. Importantly, more advanced strategies such as "Least Absolute Shrinkage and Selection Operator" (LASSO) (Tibshirani, 2018; Zhou et al., 2024) are now available, which have potential to provide more accurate data-driven feature selection compared to traditional methods, with better collinearity handling (Hammami et al., 2012) particularly in smaller datasets. However, so far these are underutilised in the behavioural sciences (McNeish, 2015). In this study, the LASSO method for feature selection is used to provide an additional data-driven approach to feature reduction and selection (Steyerberg et al., 2000).

Based on all these considerations, using data available from ADNI, the aim of this study is to address these gaps, in order to identify neuropsychological profiles of people who present with different groupings of psychotic symptoms and discuss how these differ from one another when considering their thematic component. This is achieved by separating psychotic symptoms into individual symptoms and thematic groups with clear strategies to control for the presence of the other symptoms/themes, matching the samples to participants who do not present with psychotic symptoms, on the basis of age, gender, education and disease stage. Findings are then compared between 1) a data-driven approach, based on LASSO regression, and 2) a literature-based approach, which considers both cognitive domains using confirmatory factor analysis-based composite scores, and specific functions using individual neuropsychological tests.

6.3. Methods

6.3.1. ADNI protocols and data

Data for this study was obtained from protocols 2 and 3 of the ADNI database (previously illustrated in chapter 1 and also used for the studies of chapters 2 and 4). In this case, in addition to the Neuropsychiatric Inventory (NPI), which was used to select the sample of participants with psychotic symptoms and their matched controls, the following data

was employed: the MMSE, used as a measure of disease progression, demographic features such as age at assessment of NPI, gender and education, and neuropsychological independent variables selected from the neuropsychological battery file, and the Alzheimer's Disease Assessment Scale (ADAS-Cog-13).

6.3.2. Participants

Participants were included in this study if they presented with AD dementia, or MCI due to AD, according to ADNI's criteria (*ADNI | Alzheimer's Disease Neuroimaging Initiative*, 2026). After merging of the relevant ADNI's tables only the latest visit of participants was selected, in order to capture greater variability of neuropsychiatric and neuropsychological symptoms based on disease advancement, optimising the spread of cognitive abilities (Mukherjee et al., 2023). People were included who presented with psychotic symptoms, after filtering of participants with missing data on both the neuropsychological battery and the sub-tests of the ADAS-Cog-13 (full procedure to account for missingness is explained in section 6.3.6.1). From the initial pool of participants, sub-groups were formed reflecting participants who presented with delusions, hallucinations, misidentification, paranoia and delusion of theft (demographic characteristics in Table 6.1, flowchart for group selection depicted in Figure 6.1).

6.3.3. Neuropsychiatric Inventory

The NPI (Cummings et al., 1994) described in previous chapters of this thesis, was used to select participants and controls. In addition to using NPIA and NPIB for delusions and hallucinations, new columns were added to the database based on presence (1) or absence (0), corresponding to: psychosis, formed by a positive score on the items NPIA and/or NPIB; paranoia, formed by a positive answer to the delusional subtypes of fear of being in danger (NPIA1) theft (NPIA2), jealousy (NPIA3) and abandonment (NPIA7); misidentification, formed by the questions relating to hallucinations (NPIB1 to 7, as all hallucinatory sensory modality were included) in addition to the delusional subtypes of phantom boarders (NPIA4), Capgras syndrome (NPIA5), not recognising one's home (NPIA6) and television/magazine figures present in the house (NPIA8); NPIA2 was used to perform the analyses relating specifically to delusion of theft, within the subgroup of paranoid delusions. For the analyses in this chapter, subgroups were formed based on

the reported presence of each symptom classification, therefore disregarding the elements of frequency and severity that the tool provides. However, to maximise sample size, when performing analyses on the participants with delusions and hallucinations, the other symptoms were controlled for by adding the total score (i.e., NPIATOT for the hallucinations analysis and NPIBTOT for the delusions analysis) as covariates. This was not possible for the subgroups of misidentification and paranoia, and delusion of theft, which were created ad hoc with the criterion of presenting with positive scores on those items as indicated above, therefore in these cases, the uniqueness of the subgroups was obtained similarly to chapter 4, by excluding the participants (n=30) who presented with positive scores on both subtypes (participants within the paranoid subtype who presented with delusion of theft were used for the further analyses on this sub-group, but not those who presented misidentification) as well as those who only presented with positive score on the delusional subtype classed as “other” (n=13), therefore could not be identified with any of the two groups. Details on the total number of people presenting with positive score on each subtype of delusions and hallucinations are presented in Table 6.2.

6.3.4. The Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS-COG-13 (Mohs, 1994), introduced in chapters 1 and 5, is an examiner-administered test of cognitive function; it is scored in terms of errors, with a total score ranging from 0 to 85 (higher scores reflecting poorer performance). The version used in this study is composed of thirteen items with the following ranges: Q1. Word Recall (0-10), Q2. Commands (0-3), Q3. Constructional Praxis (0-4), Q4. Delayed Word Recall (0-10), Q5. Naming Objects and Fingers (0-5), Q6. Ideational Praxis (0-5), Q7. Orientation (0-8), Q8. Word Recognition (0-12), Q9. Remembering Test Instructions (0-5), Q10. Comprehension of Spoken Language (0-4), Q11. Word-finding Difficulty (0-4), Q12. Language (0-5), Q13. Number Cancellation (0-5). In this study, the individual subtest scores were employed as predictors in order to assess the value of each cognitive function tested.

6.3.5. ADNI Neuropsychological Battery

The neuropsychological battery of tests that is available via ADNI comprises tests assessing several different cognitive functions. Among these, as additional predictive

features, the following tests were selected: the Clock Drawing and Clock Copy tests (0-5, higher scores reflective of better performance); the Category Fluency – Animals (the score reflects the number of animals recollected) (Harrison et al., 2000); the Trail Making Tests - A and B (the scores reflective of the seconds employed to complete the tests); the Rey Auditory Verbal Learning Test and Rey Auditory Verbal Learning Test - Delayed (0-15, higher scores reflective of better performance) (Rey, 1958). Other tests were excluded due to their high missingness proportion (i.e., Boston Naming Test and Logical Memory, which had a proportion of missingness respectively of 45% and 29% (same for both Immediate and Delayed); Digit Span – Forward and Backward, which were not available in ADNI protocols 2 and 3).

6.3.6. Statistical analysis procedure

A dataset was created by merging all ADNI tables containing the predictors mentioned above (in Appendix D, a full list of ADNI codes and corresponding labels), in addition to demographic and diagnosis-related information, which allowed selection of the pool of participants. The outcome variables consisted of the presence vs absence of one type of psychotic symptoms as illustrated in Table 6.1. The analysis scripts were created and implemented using R (version 4.4.2) (R Core Team, 2025), in RStudio (version 2025.05.1 "Mariposa Orchid") (Posit team, 2025), and they are available in the OSF Folder linked to this thesis.

6.3.6.1. Missing data and imputation

The dataset was inspected for missing data, and the missingness issue was approached in a two-stage process: first, the columns corresponding to the Boston Naming Test and Logical Memory were eliminated due to their high proportion of missing data (as explained in section 6.3.5). Following this, the rows corresponding to each participants were inspected, and subsequently, those who did not have scores present on either the neuropsychological battery or the ADAS-Cog-13 were eliminated (Appendix D provides the proportion of missingness for each variable). Following these steps, the database still included 0.92% of missing data overall. Three imputation methods were evaluated, among which missForest (Stekhoven & Bühlmann, 2011) resulted as the best performing one for this data, according to the metrics of Average Sum of Absolute Differences (SAD) and Mean Absolute Error (MAE) (Appendix D). This method is based on Random Forest:

for each variable missForest fits a random forest on the observed part and then predicts the missing part; this is done iteratively for a set number of times. This method has also been shown to be particularly effective in scenarios such as the current one, with multivariable data consisting of continuous and categorical variables. Therefore, missing values were imputed using the missForest algorithm, set at 10 iterations and 100 estimators (decision trees), with a set seed for randomisation initialisation to ensure reproducibility, and a new database was created which was subsequently used for the analyses.

6.3.6.2. Data preparation

As mentioned in the above section on participants, after merging of tables and missing data imputation, only the latest visit was selected for all participants. Among the twenty neuropsychological independent variables, the majority had a direction of higher score equivalent to worse performance: these in fact included the two Trail Making Test scores, and all subitems of the ADAS-Cog-13. For this reason, the remaining neuropsychological tests scores were reversed, namely the two Clock score and Clock Copy scores, the Category Fluency test, and the two Rey Auditory Verbal Learning test scores. This was done to obtain consistent scores to use in the confirmatory factor analysis model, and in the interpretation of results. Furthermore, considered the variability between assessment scales employed, all scores were standardised to z-scores so that each test would contribute comparably to multivariable analyses. Lastly, for every group of participants, a set of control participants was matched using the R function MatchIt: this was done based on age, gender, education, and disease stage (either AD, or MCI due to AD).

6.3.6.3. Confirmatory factor analysis on neuropsychological variables

In order to obtain the scores corresponding to cognitive domains, two confirmatory factor analysis models were compared using the neuropsychological tests and subtests described above, adapted from Park et al. (2012), Verma et al. (2015), Siedlecki et al. (2008), Battista et al. (2017) and Mukherjee et al. (2023). This was done to test the fit in this dataset of the four-factors structure of memory, attention/executive function, visuospatial function and language. The first model included all neuropsychological items, while the second model included a more refined sub-selection for the factors of

memory and language, i.e. only including the ADAS items Q2 (Commands), Q5 (Naming Objects) and Q6 (Ideational Praxis) for language (Mukherjee et al., 2023), and the items Q4 (Delayed Word Recall), Q8 (Word Recognition) and the RAVLT Delayed for episodic memory (Siedlecki et al., 2008).

6.3.6.4. Logistic regression analysis procedure

Two models of logistic regression were created, whereby the dependent variables were the specific psychotic symptom investigated, and the independent variables 1) the composite scores corresponding to cognitive domains and 2) the individual neuropsychological tests described above, in univariable and multivariable models; all models were tested with and without MMSE as a covariate, to additionally report the value of specific neuropsychological tests in addition to overall cognitive status.

For the models which assessed the neuropsychological tests individually, cognitive functions and processes underlying the tests and sub-tests used were considered as follows: working memory/learning (Q1 from the ADAS-Cog-13 and Rey Auditory Verbal Learning Test – Immediate); verbal episodic memory (Q4 and Rey Auditory Verbal Learning Test – Delayed for recall; Q8 for recognition); visuospatial function (Q3 and Clock Drawing and Copy); receptive language (Q2, Q9, Q10); expressive language (Q5, Q11, Q12); ideational praxis (Q6); spatiotemporal orientation (Q7); attention (Q13); processing speed (Trail Making Test – part A); executive function (Trail Making Test – part B); semantic fluency (Category Fluency - Animals).

Multicollinearity of predictors was assessed using variance inflation factor (VIF between 5 and 10 was considered indicative of moderate multicollinearity, and VIF equal or greater than 10 indicative of problematic multicollinearity (Sheather, 2009)), as well as by looking at the multicollinearity tables built using pairwise Pearson correlation coefficients (as these were calculated on z-scores), whereby $|r| > 0.7$ was considered high (Dormann et al., 2013) (Appendix D).

In the regression models based on the CFA composite scores for cognitive domains (Table 6.3), no reduction of the variables was necessary, and the variables were tested in univariable and multivariable models.

In the models that tested neuropsychological tests individually, two approaches to regression were employed. First, a LASSO regression analysis was performed, in which

variable selection is achieved statistically by shrinking regression coefficients toward zero, and only the variables identified as the most informative were retained and then tested for significance (Table 6.4). Then, all variables were tested using univariable logistic regression models (Table 6.5), to assess the association between each independent variable and the classifications of psychotic symptoms (with and without MMSE as a covariate and considering *p* values uncorrected as well as after correction for multiple comparisons, FDR and FWE). All variables retained by the LASSO models, including those that were not significant in the LASSO regression, as well as the variables which were significantly associated with each symptom group when tested in univariable models were then considered for testing in multivariable models, to investigate the value of each predictor while accounting for the others (Ranganathan et al., 2017). In addition to considering significant variables from univariable models, and variables retained by LASSO regression, further selection of variables was performed in order to have an acceptable ratio of independent variable per total sample (at least ten participants presenting with symptoms of interest per predictor, 1:10 ratio (Sperandei, 2014)). When necessary, variables were therefore excluded from the models, or added to the models based on the literature findings as synthesised in chapter 5 (i.e., focusing on the variables of interest based on hypothesised associations with each symptom group), and also based on inspection of the VIF and correlation matrices (i.e., eliminating those variables which presented multicollinearity (Appendix D)).

6.4. Results

6.4.1. Descriptive statistics

The demographic features of the participants are reported in Table 6.1: the table includes both the characteristics of the overall sample of participants (n=1135), used for the factor analysis, and those of each individual regression model specifying study samples and controls.

6.4.2. Confirmatory factor analysis

Prior to running the CFA analysis, suitability was tested: the KMO statistic was 0.96, indicating excellent sampling adequacy, the MSA of individual items had all results (Kaiser, 1974), and Bartlett's test of sphericity was significant, $\chi^2(190) = 16{,}256.22$, $p<.001$ (Bartlett, 1950; Bartlett et al., 1954), indicating that the cognitive test scores were

appropriate for factor analysis. A confirmatory factor analysis was subsequently conducted to evaluate the four-factor structure representing Language, Memory, Visuospatial Function, and Attention/Executive Function (Figure 6.2). The analysis was performed using maximum likelihood estimation with robust standard errors (MLR). Among the two models tested, one inclusive of all items and one more parsimonious, with refined item selection for language and memory, the parsimonious one was chosen as it presented with improved fit indices. In fact, although the chi-square test for model fit was still statistically significant, $\chi^2(38) = 297.04$, $p<.001$ (which was expected, given the sensitivity of chi-square tests to large sample sizes), the additional fit indices were good/very good according to Hu and Bentler (1999)'s criteria: the Comparative Fit Index (CFI) was 0.966 and the Tucker–Lewis Index (TLI) was 0.950, indicating excellent comparative fit; the Standardised Root Mean Square Residual (SRMR) was 0.035, indicating very good fit; the Root Mean Square Error of Approximation (RMSEA) was 0.077, with a 90% confidence interval of [0.069, 0.086], which reflects acceptable approximate fit for applied research. All items loaded significantly onto their intended latent constructs ($p<.001$), and standardised factor loadings, as shown in Figure 6.2, were strong, indicating that each observed variable was a reliable indicator of its respective latent factor. In the parsimonious model (with refined test selection), all items presented with more consistent loadings to their domain compared to the one in which all neuropsychological tests were included. The latent factors were positively correlated, which is consistent with the theoretical expectations that cognitive domains are interrelated, and as such may have overlapping basic elements (Harvey, 2019); at the same time, neuropsychological tests, as seen in Chapter 5, tend to tap into different cognitive domains, which might contribute to explaining the high correlation among some factors (for example the Clock tests are typically used to assess visuospatial function, however they also have a substantial executive component).

Table 6.1

Participants groups and demographic features

Symptoms groups	Composition	Age, *M(SD)*	Gender	Education, *M(SD)*	Disease stage	MMSE, *M(SD)*
All participants	N=1135	76.65 (8.33)	Male 649	16.04 (2.62)	MCI 656	24.38 (5.50)
			Female 486		AD 479	
Psychotic cluster	Positive score on NPIA and/or NPIB, n=114	78.16 (7.78)	Male 58	15.32 (2.57)	MCI 13	19.01 (6.60)
			Female 56		AD 101	
Control sample for psychotic cluster	Negative score on NPIA and NPIB, n=114	78.00 (7.46)	Male 58	15.41 (2.54)	MCI 13	21.18 (5.96)
			Female 56		AD 101	
Delusions	Positive score on NPIA, n=89	78.12 (7.74)	Male 42	15.12 (2.62)	MCI 11	18.59 (6.66)
			Female 47		AD 78	
Control sample for delusions	Negative score on NPIA and NPIB, n=89	78.00 (7.44)	Male 42	15.19 (2.54)	MCI 11	21.27 (6.19)
			Female 47		AD 78	
Hallucinations	Positive score on NPIB, n=50	77.82 (7.66)	Male 26	15.76 (2.47)	MCI 4	18.10 (7.50)
			Female 24		AD 46	
Control sample for hallucinations	Negative score on NPIA and NPIB, n=50	77.76 (7.57)	Male 26	15.84 (2.48)	MCI 4	20.71 (6.71)
			Female 24		AD 46	
Misidentification	Positive scores on NPIA4,5,6,8, NPIB, n=45	78.44 (7.63)	Male 20	15.31 (2.61)	MCI 4	18.35 (7.25)
			Female 25		AD 41	
Control sample for misidentification	Negative score on NPIA and NPIB, n=45	78.42 (7.63)	Male 20	15.40 (2.53)	MCI 4	21.40 (5.52)
			Female 25		AD 41	
Paranoia	Positive scores on NPIA1,2,3,7, n=26	78.19 (8.74)	Male 14	14.92 (2.38)	MCI 3	20.65 (4.84)
			Female 12		AD 23	
Control sample for paranoia	Negative score on NPIA and NPIB, n=26	78.19 (8.12)	Male 14	15.00 (2.31)	MCI 3	20.61 (4.84)
			Female 12		AD 23	
Delusion of theft	Positive score on NPIA2, n=19	79.42 (8.08)	Male 9	14.21 (2.04)	MCI 2	19.42 (6.27)

Symptoms groups	Composition	Age, *M(SD)*	Gender	Education, *M(SD)*	Disease stage	MMSE, *M(SD)*
			Female 10		AD 17	
Control sample for delusion	Negative score on NPIA and NPIB,	79.47 (8.70)	Male 9	14.10 (2.10)	MCI 2	20.78 (4.57)
of theft	n=19		Female 10		AD 17	

Abbreviations. NPIA = delusions; NPIA1 = delusion of harm; NPIA2 = theft, NPIA3 = jealousy, NPIA4 = Capgras syndrome, NPIA5 = phantom boarders, NPIA6 = not recognising one's home; NPIA7 = abandonment; NPIA8 = television/magazine figures present in the house; NPIB = hallucinations; MMSE = mini mental state exam; M = mean; SD = standard deviation.

Table 6.2

Total numbers of people presenting with delusions and hallucinations subtypes from the NPI

NPI code	Subtype	N tot
NPIA1 (P)	Fear of being in danger/ being harmed	16
NPIA2 (P)	Theft	42
NPIA3 (P)	Jealousy	10
NPIA4 (M)	Phantom boarders (intruders living in the house)	17
NPIA5 (M)	Capgras syndrome	18
NPIA6 (M)	Not recognising one's home	24
NPIA7 (P)	Fear of abandonment	15
NPIA8 (M)	Images from TV or magazines present in the house	10
NPIA9	Other	30
NPIB1	Hearing voices/sounds	18
NPIB2	Talking to people who are not there	16
NPIB3	Seeing people/things not seen by others	41
NPIB4	Smelling odors not smelled by others	1
NPIB5	Tactile feelings	6
NPIB6	Tastes without known cause	1
NPIB7	Other	8

Notes. The total number for each subtypes is derived from the total (psychotic cluster) group. (P) indicates delusions relating to the subtype of paranoia, (M) misidentification.

Figure 6.1

Flowchart for group inclusion

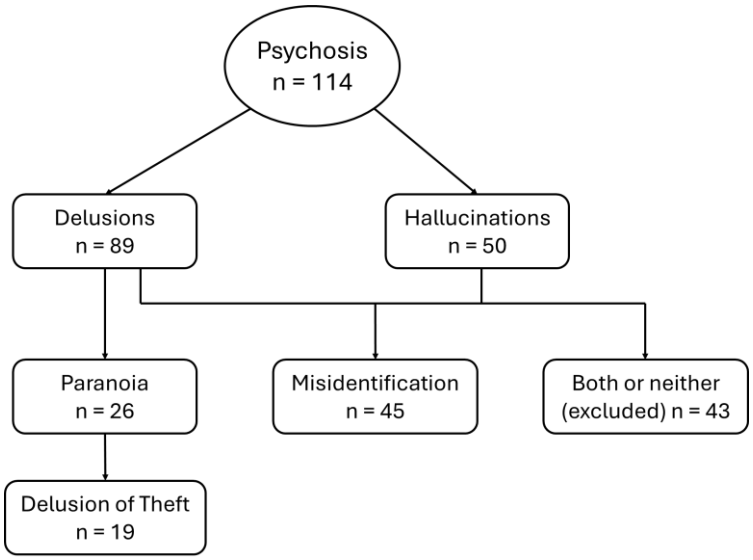
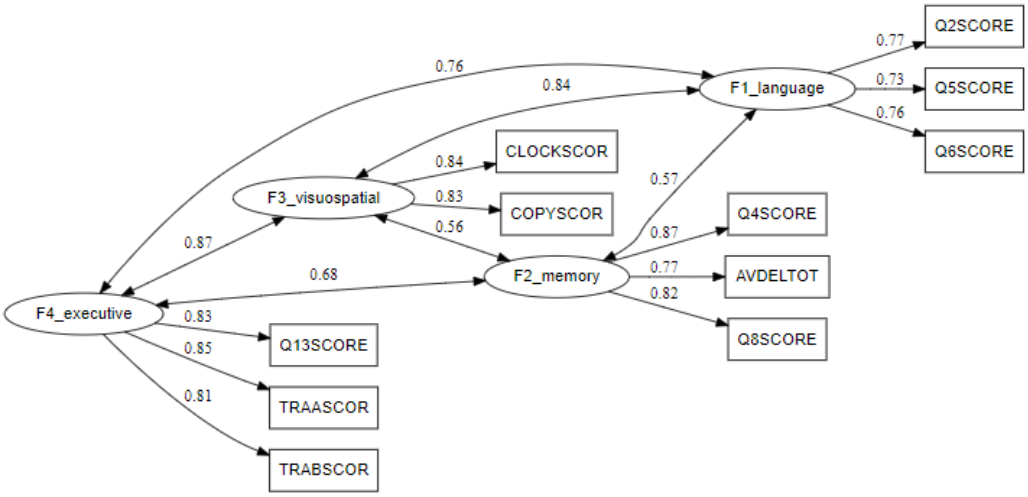


Figure 6.2

Confirmatory factor analysis structure



Notes. The items chosen for the CFA are as follows: for the Attention/Executive function domain, Number Cancellation (Q13), and the Trail Making Tests A and B; for the Visuospatial Function, the Clock Drawing and Copy test; for Memory Delayed Word Recall (Q4) from ADAS-Cog-13 and Rey Auditory Verbal Learning Test (Q4 and AVDELTOT) and Word Recognition (Q8); for Language Commands, Naming Objects and Fingers and Ideational Praxis (Q2, Q5, Q6).

6.4.3. Regression analyses

6.4.3.1. Logistic regression models based on CFA composite scores

The four composite scores created using the items of the CFA were used as independent variables in models with different groups of psychotic symptoms. Univariable models, in which each composite score was investigated independently, identified associations in relation to most groups: when considered as a cluster, psychosis was associated with language, visuospatial and executive function; delusions with episodic memory; hallucinations with visuospatial and executive functions; misidentification with all four domains; paranoia and delusion of theft had no significant predictors (Table 6.3). The multivariable analyses (in which all four factors were used in the models as independent

variables entered at the same time) were significant for all the above symptom groups as follows: psychotic cluster $\chi^2(4) = 14.18$, p=.0067, Nagelkerke R^2 = .08; delusions $\chi^2(5) = 18.58$, p=.0023, Nagelkerke R^2 = .132; hallucinations $\chi^2(6) = 21.157$, p=.0017, Nagelkerke R^2 = 0.254; misidentification $\chi^2(4) = 12.507$, p=.014, Nagelkerke R^2 = .08; however, there was not a significant contribution from any variable in any of the groups (all reported in Appendix D). Analyses for the paranoia and delusion of theft were not run due to the small sample size in these sub-groups and as the univariable analyses did not identify any significant predictors.

Table 6.3

Univariable models of individual predictors based on CFA logistic regression

Cognitive domain	Psychotic cluster	Delusions	Hallucinations	Misidentification
Episodic Memory	-	OR = 1.64, CI [1.02, 2.71], *p* = .0440	-	OR = 2.283, CI [1.198–4.615] *p* = .0155**
Language	OR = 1.371, CI [1.042, 1.834], *p* = .0281 *	-	-	OR = 2.128, CI [1.257–3.967) *p* = .0092**
Visuospatial Function	OR = 1.532, CI [1.174, 2.025], *p* = .0021 *	-	**OR = 1.643, CI [1.093, 2.534], *p* = .0196 ***	OR = 1.967, CI [1.247–3.259] *p* = .0054**
Attention/Executive Function	**OR = 1.691, CI [1.24, 2.335], *p* = .0011 ****	-	**OR = 1.932, CI [1.179, 3.275], *p* = .0109 ****	**OR = 2.49, CI [1.442–4.558] *p* = .0017****

Notes. Uncorrected p values are reported here, however * indicates the predictor was significant with FDR correction and ** indicates the predictor was also significant with FWE Holm-Bonferroni correction (as well as FDR) and in bold are the predictors which remained significant when MMSE was included as a covariate. For the subgroups of delusions and hallucinations, NPIBTOT and NPIATOT were always included as covariate to control for the presence of the other symptom. Extended results tables are presented in Appendix D, which include corrected *p* values and unsignificant results. *Abbreviations*. OR = odds ratio; CI = confidence interval (95%).

6.4.3.2. Logistic regression models based on individual cognitive tests

Within the LASSO models, all predictors were entered simultaneously, so that only the most relevant variables would be retained. Table 6.4 illustrates this, indicating which variables were retained in the models and among these, which resulted as significantly associated with the symptoms. Variables selected with this method were then considered for the multivariable logistic regression models.

Subsequently, all variables were tested individually (Table 6.5); lastly, multivariable models were created, where relevant predictors based on LASSO selection, univariable analysis and the literature were entered simultaneously. Due to the limited sample sizes for the different sub-groups of psychotic symptoms, the number of independent variables considered differed across models. For two of the groups, paranoia and delusion of theft, multivariable models were not performed due to the small sample size and high collinearity among predictors in the VIF analysis, as illustrated below.

The results from all the approaches are summarised in Table 6.6.

Considering the psychotic cluster, LASSO regression retained the variables Q10 (Comprehension of Spoken Language), the Clock Copy, and both A and B of the Trail Making Test (though none were significant in the model); the univariable analyses also identified these predictors, and in addition Q6 (Ideational Praxis), Q7 (Orientation), Q9 (Remembering Test Instructions), Q12 (Language), Q13 (Number Cancellation), Clock Drawing, Immediate Rey Auditory Verbal Learning Test and Category Fluency before controlling for MMSE; Q7 (Orientation), Q10 (Comprehension of Spoken Language), Q13 (Number Cancellation), Clock Drawing and Trail Making Test B survived FDR correction, and the Clock Copy and Trail Making Test A were also significant when including MMSE as a covariate and they also survived Holm-Bonferroni correction. All these tests with the exception of Q9 (Remembering Test Instructions) and Q12 (Language), due to multicollinearity with Q10 (Comprehension of Spoken Language), were used in the multivariable analysis, with the addition of Q4 (Delayed Word Recall) based on the literature (from chapter 5); the model was not significant ($\chi^2(10) = 16.04$, p=.0986, Nagelkerke R^2 = .091) and no predictor showed a significant independent effect (Appendix D).

The delusions LASSO model identified Q4 (Delayed Word Recall), Q10 (Comprehension of Spoken Language), Q12 (Language), Clock Copy, Immediate Rey Auditory Verbal Learning Test and Trail Making Test A (none was significant). The univariable models also identified Q4 (Delayed Word Recall), Q10 (Comprehension of Spoken Language) and Clock Copy, and in addition Q1 (Word Recall) and Q7 (Orientation); none survived correction, and only Q4 (Delayed Word Recall) remained significant when controlling for the MMSE total score. All tests except Q10 (Comprehension of Spoken Language) and the Immediate Rey Auditory Verbal Learning Test were included in the multivariable analysis which, following the literature, also included the Category Fluency Test and Trail Making Test Part B. The model was significant overall ($\chi^2(11) = 23.86$, p=.0133, Nagelkerke $R^2 = 0.167$), but no predictor showed a significant independent effect with the exception of Q4 (Delayed Word Recall) which was a significant independent predictor (OR = 2.078, CI [1.023, 4.422], p=.0486) in the model run while covarying for MMSE (table of results in Appendix D).

The LASSO model for hallucinations identified the Clock Copy and both Trail Making Tests A and B; these three tests were significant in the univariable analyses, which additionally identified Q13 (Number Cancellation), (all four predictors were significant also while covarying for MMSE, however none survived correction for multiple comparisons). Due to the smaller sample size in this group, only these four tests and Q5 (Naming Objects) as a measure of language based on the literature were used for the multivariable analysis, which was significant overall ($\chi^2(7) = 21.17$, p=.0035, Nagelkerke $R^2 = .0035$), but no predictor showed a significant independent effect.

The LASSO model for misidentification identified a number of predictors positively associated with the symptom: Q5 (Object Naming), Q6 (Ideational Praxis), Q7 (Orientation), Q10 (Comprehension of Spoken Language), Q13 (Number Cancellation), Trail Making Test part B). The univariable analyses identified Q5 (Object Naming), Q6 (Ideational Praxis), Q7 (Orientation), Q10 (Comprehension of Spoken Language), Q13 (Number Cancellation), Trail Making Test part A and B, Clock Drawing and Copy and Category Fluency; only Q13 (Number Cancellation) and the Trail Making Test part B were also significant when MMSE was entered as a covariate and survived FDR correction for multiple comparisons, while only Q13 (Number Cancellation) also survived Bonferroni-Holm correction. In this case, the tests entered in the multivariable model were Q7

(Orientation), Q10 (Comprehension of Spoken Language), Q13 (Number Cancellation) and the two Trail Making Test scores; the model was significant ($\chi^2(6) = 19.299$, p=.0037, Nagelkerke R^2 = .257), with Q13 (Number Cancellation) as significant independent predictor (OR = 2.082, CI = 1.090-4.248, p=.0326) when covarying for MMSE.

Q4 (Delayed Word Recall) emerged as significant from the paranoia LASSO model. This was also predictor in the univariable analysis and significant when controlling for MMSE; the univariable analysis also identified Q3 (Constructional Praxis) negatively associated with the symptom. The VIFs in this model were >10 on most variables except Q10 (Comprehension of Spoken Language), Q13 (Number Cancellation), and the Auditory Verbal Learning Test – Immediate and Delayed. Multivariable analysis was not run on this group due to the small sample size and high multicollinearity among variables.

Lastly, no predictors emerged for delusion of theft in LASSO, nor in the univariable analyses. All predictors in this group had VIF>10. Similarly to the paranoia group, multivariable analysis was not run on this group due to the small sample size and high multicollinearity among variables.

Table 6.4

LASSO selected predictors (retained and significant)

Neuropsychological Test	Psychotic cluster	Delusions	Hallucinations	Misidentification	Paranoia	Delusion of theft
Word Recall	-	-	-	-	-	-
Commands	-	-	-	OR = .447, CI [.212–.861], *p* = .0224	-	-
Constructional Praxis	-	-	-		OR = .414, CI [.193–.784], *p* = .0121	-
Delayed Word Recall	-	OR = 1.467, CI [.907–2.497], *p* = .1341	-	OR = .499, CI [.189–1.244], *p* = .1385	**OR = 3.727, CI [1.421–12.734], *p* = .0165**	-
Naming Objects and Fingers	-	-	-	OR = 1.510, CI [.798–3.010], *p* = .2171	-	-
Ideational Praxis	-	-	-	OR = 1.234, CI [.772–2.064], *p* = .3938	-	-
Spatiotemporal Orientation	-	-	-	OR = 1.724, CI [.810–3.943], *p* = .1719	-	-
Word Recognition	-	-	-		-	OR = .683, CI [.408–1.111], *p* = .1316
Remembering Test Instructions	-	-	-	OR = .497, CI [.251–.885], *p* = .0273	-	-
Comprehension of Spoken Language	OR = 1.109, CI [.887–1.394], *p* = .3679	OR = 1.042, CI [.754–1.445], *p* = .8046	-	**OR = 2.258, CI [1.191–4.895], *p* = .0221**	-	-
Word-finding Difficulty	-	-	-	-	-	-
Language	-	OR = 1.084, CI [.797–1.479], *p* = .606	-	-	-	-
Number Cancellation	-	-	-	**OR = 3.450, CI [1.657–7.972], *p* = .0018**	-	-

Neuropsychological Test	Psychotic cluster	Delusions	Hallucinations	Misidentification	Paranoia	Delusion of theft
RAVLT Immediate	-	OR = 1.086, CI [.715–1.655], *p* = .698	-	OR = .549, CI [.229–1.218], *p* = .1542	-	-
Clock Drawing	OR = 1.174, CI [.889–1.557], *p* = .2591	OR = 1.096, CI [.795–1.514], *p* = .5742	OR = 1.28, CI [.899–1.85], *p* = .1737	-	-	-
Clock Copy	-	-	-	-	-	-
Category Fluency	-	-	-	-	-	-
TMT-A	OR = 1.157, CI [.847–1.597], *p* = .3645	OR = 1.138, CI [.833–1.567], *p* = .4212	OR = 1.1, CI [.684–1.769], *p* = .6914	-	-	-
TMT-B	OR = 1.141, CI [.793–1.646], *p* = .4778	-	OR = 1.57, CI [.868–2.964], = .1454	OR = 1.319, CI [.651–2.732], *p* = .4439	-	-
RAVLT Delayed	-	-	-	-	-	-

Notes. All variables retained by the LASSO regression are reported as predictive of each classification of psychotic symptoms. In bold, are those that within each LASSO regression model were also significantly associated with the symptom of interest. *Abbreviations*. OR = odds ratio; CI = confidence interval (95%); RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test.

Table 6.5

Univariable logistic regression results

Neuropsychological test	***P*sychotic cluster**	**Delusions**	**Hallucinations**	**Misidentification**	***P*aranoia**	**Delusion of Theft**
Word Recall	-	OR = 1.544 , CI [1.109 2.186], *p* = .0116	-	-	-	-
Commands	-	-	-	-	-	-
Constructional Praxis	-	-	-	-	**OR = .52, CI [.27, .93], *p* = .0356**	-
Delayed Word Recall	-	**OR = 2.049 , CI [1.271 3.519], *p* = .0053**	-	-	**OR = 2.75, CI [1.11, 8.56], *p* = .0486**	-
Naming Objects and Fingers	-	-	-	OR = 1.48, CI [1.04, 2.24], *p* = .0430	-	-
Ideational Praxis	OR = 1.246, CI [1.038 1.514], *p*= .0211	-	-	OR = 1.58, CI [1.16, 2.28], *p* = .0073 *	-	-
Spatiotemporal Orientation	OR = 1.391, CI [1.088 1.791], *p* = .0093 *	OR = 1.38 , CI [1.038 1.852], *p* = .0284	-	OR = 1.67, CI [1.10, 2.62], *p* = .0198	-	-
Word Recognition	-	-	-	-	-	-
Remembering Test Instructions	OR = 1.201, CI [1.004 1.447], *p*= .0485	-	-	-	-	-
Comprehension of Spoken Language	OR = 1.29, CI [1.069–1.577], *p* = .0098 *	OR = 1.258 , CI [1.011 1.593], *p* = .0453	-	OR = 1.60, CI [1.16, 2.35], *p* = .0083 *	-	-
Word-finding Difficulty	-	-	-	-	-	-
Language	OR = 1.244, CI [1.036–1.515], *p* = .0232	-	-	-	-	-
Number Cancellation	OR = 1.359, CI [1.07–1.737], *p* = .0129 *	-	OR = 1.56, CI [1.075, 2.308], *p* = .0216	**OR = 2.12, CI [1.40, 3.37], *p* = .0007 ****	-	-
Clock Drawing	OR = 1.335, CI [1.067–1.68], *p* = .0124 *	-	-	OR = 1.52, CI [1.06, 2.20], *p* = .0245	-	-

Neuropsychological test	***P*sychotic cluster**	**Delusions**	**Hallucinations**	**Misidentification**	***P*aranoia**	**Delusion of Theft**
Clock Copy	**OR = 1.406, CI [1.152–1.731], *p* = .001 ****	OR = 1.288 , CI [1.025 1.634], *p* = .0326	OR = 1.423, CI [1.066, 1.929], *p* = .019	OR = 1.48, CI [1.08, 2.08], *p* = .0193	-	-
RAVLT Immediate	OR = 1.424, CI [1.044–1.961], *p* = .0275	-	-	-	-	-
Category Fluency	OR = 1.415, CI [1.044–1.942], *p* = .0278 *	-	-	-	-	-
TMT-A	**OR = 1.434, CI [1.148–1.815], *p* = .002 ****	-	OR = 1.519, CI [1.074, 2.196], *p* = .0212	OR = 1.55, CI [1.07, 2.31], *p* = .0240	-	-
TMT-B	OR = 1.509, CI [1.136–2.02], *p* = .005 *	-	OR = 1.975, CI [1.187, 3.506], *p* = .0127	**OR = 2.02, CI [1.24, 3.49], *p* = .0073 ***	-	-
RAVLT Delayed	-	-	-	-	-	-

Notes. Uncorrected p values are reported here, however * indicates the predictor was significant with FDR correction and ** indicates the predictor was also significant with FWE Holm-Bonferroni correction (as well as FDR) and in bold are the predictors which remained significant when MMSE was included as a covariate. For the subgroups of delusions and hallucinations, NPIBTOT and NPIATOT were always included as covariate to control for the presence of the other symptom. Extended results tables are presented in Appendix D, which include corrected p values and unsignificant results. *Abbreviations*. OR = odds ratio; CI = confidence interval (95%); RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test.

Table 6.6

Summary of all models

	Psychosis	Delusions	Hallucinations	Misidentification	Paranoia
Neuropsychological Test					
Word Recall		+			
Commands					
Constructional Praxis					
Delayed Word Recall		* + ✓			* +
Naming				* +	
Ideational Praxis	+			* +	
Orientation	+	+		* +	
Word Recognition					
Test Instructions	+				
Comprehension	* +	* +		** +	
Word-finding Difficulty					
Language	+	*			
Number Cancellation	+		+	** + ✓	
Clock Drawing	+			+	
Clock Copy	* +	* +	* +	+	
RAVLT Immediate	+	*			
Category Fluency	+				
TMT-A	* +	*	* +	+	
TMT-B	* +		* +	* +	
RAVLT Delayed					
Cognitive Function					
Memory		+		+	
Language	+			+	
Visuospatial Function	+		+	+	
Attention/Executive Function	+		+	+	

Notes. The variables associations here are only those in which greater impairment on a neuropsychological test is indicative of greater probability of presenting with a psychotic symptom group. *LASSO (selected); **LASSO (significant); +significant in the univariable model; ✓Significant in the Multivariable. *Abbreviations*. RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test.

6.5. Discussion

To the author's knowledge, this is the first study to investigate the neuropsychological correlates of psychotic symptoms in AD, while considering the different psychotic phenomena, with strict criteria to account for the neuropsychiatric profiles, as well as comparing the results of a data-driven approach based on LASSO regression, and literature-based approaches based on CFA and manual selection of predictors.

Overall, the results seemed to mostly confirm what has been reported in the literature, as seen in the systematic review reported in chapter 5. A substantial degree of agreement was also found among the different methodological approaches, which highlighted the contribution of some specific cognitive functions in relation to the different symptoms.

6.5.1. Psychotic cluster

When considered as a cluster, psychosis was associated with a broad range of functions, including measures of processing speed, executive function, attention, working memory, expressive and receptive language, visuospatial function, spatiotemporal orientation and semantic fluency; interestingly, no differences were found in this larger group on measures of episodic memory.

As seen in the previous chapter, an overall impaired neuropsychological profile was evident when considering psychotic cluster, with no marked contribution from a specific function as was seen with the different thematic manifestations. While this is in line with the notion that psychosis presents with greater cognitive load (Fuller et al., 2019), these results also appear to confirm the hypothesis that investigating the discrete manifestations might be more useful to identify clearer neuropsychological profiles.

6.5.2. Delusions

Relevant predictors associated with the sub-group of delusions largely confirmed what found previously in the literature with respect to the role of different aspects of memory, such as working memory/learning (Castelluccio et al., 2020), recall (Fischer et al., 2006) and spatiotemporal orientation (Sultzer et al., 2014). Episodic memory appeared particularly relevant in all models: in the CFA model, it was the only factor significantly associated with delusions, and the item of Delayed Word Recall of the ADAS-Cog-13 was

the only one which remained significant when covarying for MMSE score (therefore over and above overall cognitive impairment), and it was a significant independent predictor in the multivariable model.

Previous studies also found impairment in the part A of the Trail Making Test, and measures of receptive language (Castelluccio et al., 2020; Migliorelli et al., 1995) however in the current study these did not survive corrections for multiple comparisons.

A measure of visuospatial function, the Clock Copy was identified in this study, constituting an element of novelty, as this has not typically been identified in relation to delusions. However, using the same dataset (albeit with a smaller sample due to availability of MRI data) the analyses performed in chapter 4 of this thesis identified significant associations between delusions and greater atrophy in the occipital lobe; this is consistent with the literature suggesting that greater occipital atrophy correlates with more marked visuospatial difficulties in AD (Putcha et al., 2019; Rehan et al., 2021): it would appear that within this study's sample, delusions are also related to this aspect, while controlling the presence of hallucinations, which would be interesting to explore further.

6.5.3. Hallucinations

As seen in chapter 5, few studies so far have focused on investigating the correlates of hallucinations. Using similar batteries of tests as the one available for this investigation, Lü et al. (2021) and Quaranta et al. (2015) also found associations with the domains of cognition as found in this study. Specifically, of particular importance here appeared to be the Clock Copy and both Trail Making Tests A and B (the latter particularly noteworthy as it survived corrections), highlighted both by the LASSO and univariable models, with further contributions from the number cancellation item of the ADAS in the univariable model. With respect to the analysis of domains, this confirmed the role of greater visual and executive impairment, which survived correction for multiple comparison and were significant also while covarying for MMSE.

The results of this study appear to suggest that tests which rely on visual and attentional and executive abilities might present greater impairment in association with the presence of hallucinatory symptoms.

6.5.4. Misidentification

Overall, the misidentification subtype appeared more greatly impaired than the other groups, which is in line with previous literature (Pearce et al., 2022). All cognitive domains were significantly associated with this symptom, also surviving corrections for multiple comparisons, with the executive functions also significant while covarying for MMSE score. This is reflected mostly in the individual test analyses, as several associations were identified both from the LASSO regression and univariable analysis. Particularly, in addition to what was previously identified in the literature, associations were found with language-related items such as object naming and particularly comprehension of spoken language (significant in LASSO as well), as well as ideational praxis and spatiotemporal orientation.

On the other hand, in line with most literature (e.g. Perez-Madriñan et al., 2004; Reeves et al., 2015), significant associations were found in Clock Drawing and Copy, and measures of processing speed and executive function (Trail Making Test, particularly part B which survived corrections for multiple comparisons and covarying for MMSE), and attention (Number Cancellation Test from the ADAS).

Among all predictors, the Number Cancellation appeared as the most relevant, significant in all analyses, accounting for corrections, and including the multivariable regression. Quaranta et al. (2015) found comparable findings with the use of a similar test, the Multiple Features Targets Cancellation; it is important to note that both these tests heavily rely on intact visual ability. As seen in the above section on hallucinations, it would appear that these symptoms tend to associate with worst performance on tests that assess visuospatial ability among other functions, which is consistent with the findings on greater atrophy in brain areas linked to diminished sensory processing of visual stimuli (Zhang et al., 2023).

Therefore, the results of this study seem to suggest that whilst an overall impaired neuropsychological profile might be present in association with misidentification compared to controls, attentional and visual difficulties might be key components linking to and helping to explain this symptom class (Pearce et al., 2022).

6.5.5. Paranoia and delusion of theft

As expected, the analyses on paranoid delusions and delusion of theft specifically did not yield many significant associations. This is mostly in line with the literature (Perez-Madriñan et al., 2004; Quaranta et al., 2015; Reeves et al., 2015), as the studies that investigated both paranoia and misidentification, and also performed analyses to directly compare these two groups, found that people with paranoid-based delusions had a relatively unimpaired neuropsychological profile. Here no associations were found between paranoia or theft delusions with any cognitive domains in the CFA analysis; when investigating the specific tests, only delayed recall was retained and significant in the LASSO model, and it had significant univariable association with paranoid delusions (it did not however survive corrections). Interestingly, the presence of paranoia was associated with less impairment on visuoconstructional skills, which has been previously suggested (Quaranta et al., 2015). Furthermore, looking at the MMSE scores in Table 6.1 and Appendix D, these two groups were the only ones in which there were no significant differences in the global cognitive status compared to controls. While it is important to consider sample sizes for these analyses, which was smaller compared to all other groups, it is interesting to reflect on the notion that a smaller degree of cognitive impairment might be associated with these delusional subtypes compared to controls.

6.5.6. Limitations

A first limitation to consider concerns the limited availability of neuropsychological tests that are available on ADNI, and the high proportion of missing data in some tests that led to their a-priori exclusion. For these reasons, the ADAS-Cog-13 items constituted the majority of predictors, alongside available tests from the neuropsychological battery. While the ADAS-Cog-13 is not typically used with respect to its subtest isolation but mainly as an overall measure (Harrison, 2022), it is hypothesised that the careful selection of predictors which considers multicollinearity, and adding in the analyses further tests from the neuropsychological battery (Skinner et al., 2012) justify its use in this context. There was also a paucity of executive function measures available from the ADNI protocols with the exception of the Trail Making Test part B; considered the relevance these hold in association with psychosis as seen in previous chapters, this constituted a relevant limitation in the methodology of this study.

Other limitations, as seen in previous chapters where the ADNI dataset was used, include sample availability and composition, and the lack of generalisability of the ADNI database. While sample size was larger than most studies that employ local recruitment strategies, as evidenced in the previous chapter, when refining for specific themes this was still quite small to run multivariable analyses with different predictors. In order to maximise sample size MCI participants were included in the analyses, however with larger samples available it would be useful to stratify for disease stage. As mentioned in the study limitations presented in chapter 4, the neuropsychiatric inventory that is the source of information on psychotic symptoms, within the ADNI protocol is administered yearly with reflection over the previous 4 weeks: it is possible that a more frequent assessment would allow for a more precise classification of the symptoms, thus aiding in these types of analyses which aim to clarify their underlying mechanisms.

6.6. Conclusions

The findings of this study indicate that psychosis tends for the most part to be associated with greater cognitive dysfunction, and in confirmation of the hypothesis, clarity over which specific functions correlate with psychotic symptoms is achieved when considering distinct manifestations. Different methodological approaches to neuropsychological assessment largely yielded comparable results, and these were mostly in line with previous literature (e.g., delusions are associated with impaired episodic memory, hallucinations and misidentification with visuospatial and attentional components), with some novel elements, such as a link between delusions and visuospatial function. Despite its limitations, this study provided evidence of an association between different aspects of cognitive function and the various psychotic symptom presentations in AD, which confirms the relevance of these symptoms within the AD clinical picture, as well as suggesting potential cognitive predictors of psychosis in AD, which could be further explored in assessment and treatment studies.

Chapter 7 – Study 4: Random forest classifiers using multimodal data to predict psychotic symptoms in Alzheimer's disease

7.1. Overview

In previous chapters of this thesis, the study on the association of psychotic symptoms in Alzheimer's Disease (AD) has been approached from a neuropsychiatric, neuroanatomical and neuropsychological perspective. In chapter 2, a factor analysis was performed on the items of the Neuropsychiatric Inventory (NPI), to clarify the stability of neuropsychiatric clusters over time; key findings in relation to psychotic symptoms indicated that delusions and hallucinations tend to cluster over time in AD (although not exclusively), and that particularly at later stages, they also cluster with other symptoms, mostly depression, anxiety, agitation, irritability and sleep disorders. In chapters 3 and 4, the neuroanatomical associations of psychotic symptoms were explored with a systematic review and an independent study, which highlighted the presence of greater atrophy in fronto-temporal and occipital areas in association with most psychotic symptoms. Lastly, in chapters 5 and 6, a systematic review and an independent study were presented which indicated that greater impairment mostly on measures of memory, executive function, attention and visuospatial function tend to relate to psychotic symptoms. In this study, the first aim of this thesis, that of clarifying the underlying mechanisms of psychotic symptoms, is approached using a predictive model, as introduced in chapter 1. This is done using a machine learning method, Random Forest (RF) analysis, to investigate the combinatorial value of neuroanatomical, neuropsychological, and neuropsychiatric features (objective 6 of this thesis). The Alzheimer's Disease Neuroimaging Initiative (ADNI) provided the data. The Neuropsychiatric Inventory (NPI) identified participants with and without psychotic symptoms. Multimodal predictors included: other neuropsychiatric symptoms; neuropsychological tests and sub-tests; FreeSurfer-derived brain metrics. RF classification with 5-fold cross-validation was used alongside feature importance ranking. The resulting model was robust (average cross-validation (CV) accuracy: 74%) in predicting psychosis. The most predictive variables were memory, executive function and anxiety, and key neuroanatomical contributors included the right amygdala, right inferior and medial temporal, left rostral and caudal mid-frontal and left entorhinal cortex. The results of this study suggest that RF machine learning can be used to

advance the understanding of the complex interaction of predictors of psychotic symptoms in AD.

7.2. Introduction

In the previous chapters, the underlying mechanisms of psychotic symptoms in AD have been approached from single viewpoints, addressing the questions on the associations of different manifestations of psychosis. As discussed in chapter 1, a different, complementary approach is that of predicting the presence of these symptoms, based on the premise that the likelihood of presenting with psychotic symptoms is related to a complex combination of neuroanatomical, cognitive, neuropsychiatric, genetic/ epigenetic, and neurobiological vulnerability factors, as well as environmental and contextual triggers (as shown in Figure 1.1 from the first chapter). It was there discussed that previous studies have suggested that one key means to understanding the causes of psychotic phenomena in AD might lie in the interaction between their underlying mechanisms (Ballard et al., 2020; El Haj et al., 2017; Ismail et al., 2022), indicating the need for the application of comprehensive models (e.g., Looijestijn et al., 2015) specific to the manifestation of these symptoms in AD. Particular attention should be given to the distinction between trait markers (such as cognitive deficits, brain atrophy or genetic predisposition), and state markers (e.g., psychological distress or iatrogenic factors which trigger each manifestation of the symptoms) (El Haj et al., 2017) in explaining the fluctuation of psychotic phenomena through the AD continuum, and also in other types of dementia. This has potential to improve treatment strategies, as combined interventions aimed at different components might have synergistic benefits (Collerton et al., 2023).

Rationale for the current study is thus rooted in the exploration of previously identified vulnerability factors in a complex, multifactorial predictive model of psychosis. Specifically, in chapters 1 and 2 it was highlighted that psychotic symptoms in AD are often found alongside other neuropsychiatric symptoms, such as affection, sleep disorders, disinhibition, irritability, agitation and apathy therefore all other neuropsychiatric symptoms measured by the NPI were included in this model.

Table 7.1

Summary of key brain areas and cognitive functions

	Findings of Previous Reviews	Findings of the Systematic Reviews	Empirical findings
Brain areas		Psychotic cluster associated with fronto-temporal lobe and the salience network	Psychotic cluster associated with left fronto-temporal and right frontal areas
	Delusions associated with right fronto-temporal lobe and salience network	Delusions associated with right fronto-temporal areas and salience network	Delusions associated with fronto-temporal and occipital areas
	Hallucinations associated with anterior-posterior neural network, insula	Hallucinations associated with frontal and occipital lobe and anterior cingulate cortex	Hallucinations associated with the cerebellum
		Misidentification associated with fronto-temporal and occipital areas	Misidentification associated with the cerebellum and frontal areas
		Paranoia associated with temporal areas	Paranoia associated with frontal areas
Cognitive functions		Psychotic cluster associated with executive function and semantic memory	Psychotic cluster associated with overall greater cognitive dysfunction
	Delusions associated with executive function, memory, attention	Delusions associated with executive function and episodic memory	Delusions mostly with episodic memory
	Hallucinations associated with memory, attention, visuospatial function	Hallucinations associated with language and attention	Hallucination associated with attention and visuospatial function
		Misidentification associated with visuospatial function, semantic memory and attention	Misidentification associated with attention and visuospatial function
		Paranoia seldom associated with cognitive dysfunction	Paranoia relatively preserved cognition

Among neuroanatomical elements, brain regions across all four lobes, the insula, the cingulate and entorhinal cortices, as well as sub-cortical areas such as the putamen are identified across the literature, as outlined in chapters 3 and 4 of this thesis, therefore the contributions of these will be investigated in the current study alongside other factors.

Similarly, as discussed in chapter 5 and 6, the literature has identified a selection of neuropsychological tests and batteries reflecting the cognitive domains found to correlate with psychosis, such as executive function, attention, episodic and working memory, information processing speed, visuospatial ability and language.

In order to explore the interaction of these mechanisms, Random Forest (RF) analysis (Breiman, 2001) was chosen, one of the main machine learning methods which allows investigation of prediction problems using multidomain data and broad feature sets. Random Forest is a classifier which consists of a collection of deep-grown survival decision trees that can achieve low bias, and on which the output of Random Forest is synthesized (Ishwaran et al., 2021). It is an ensemble learning method, where multiple decision trees work together to produce a more accurate and stable prediction, that can lead to excellent predictive performance (Antoniadis et al., 2024) and good handling of multicollinearity, particularly in relation to model accuracy (Yarkoni & Westfall, 2017).

Its use within the field of AD has been proven effective by previous studies which investigated predictive features as neurodegenerative disease biomarkers (for instance looking at structural imaging and other biomarkers to predict progression to AD (e.g., Dimitriadis and Liparas (2018); Song et al. (2023)) or in the context of neuropsychiatric symptoms (Mar et al., 2020), to predict their prevalence, and it is considered a suitable tool to model complex, heterogeneous and high-dimensional clinical datasets (Spooner et al., 2020). To the author's knowledge, however, no previous study has employed this method to investigate multidomain predictors of psychosis in Alzheimer's disease.

Given its ability to include several, inter-related predictors it was considered a valuable technique to explore the aim of this study, which is to create a model that accounts for the combinatorial value of neuroanatomical, neuropsychological, and other neuropsychiatric features when predicting the presence of psychotic symptoms in AD.

7.3. Methods

7.3.1. Alzheimer's Disease Neuroimaging Initiative (ADNI)

The data was obtained from ADNI (*ADNI | Alzheimer's Disease Neuroimaging Initiative*, 2026), introduced in previous chapters, specifically ADNI 2 and 3 protocols. Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) data was used to identify those participants who presented with psychotic symptoms, which constituted this study sample, against those who did not, from which the control sample was selected. NPI data featuring other neuropsychiatric symptoms outside of psychosis was used as predictors, as were available metrics that were derived from the MRI scans using FreeSurfer, providing an indication of potential neuroanatomical differences, and neuropsychological test data which provided a set of cognitive predictors. In Appendix E the codes are provided for all the corresponding labels of the predictors used in the analyses.

7.3.2. Participants

Ninety-five participants identified to have symptoms of psychosis were included in this study. Of those people forty-eight participants were female and forty-seven were male; they had a mean education of 15.62 (SD=2.61). Considered the nature of the investigation, participants (n=34) who presented with psychotic symptoms at different timepoints were included so that the same person could feature in the sample at more than one instance. This is because their features relating to the predictors (e.g., scores on the cognitive tests and brain volume) are likely to differ across timepoints due to the disease process, and this may be informative when considering those relevant predictors. Considering from now on the sample as a whole, this consisted of one hundred and forty instances where either delusions, hallucinations, or both were presented, based on their scores on the NPI (Cummings et al., 1994). Of these, considering all visits (regardless of timepoint), there were one hundred and three instances of positive scores on delusions, and sixty-two on hallucinations; twenty-six of these presented both symptoms at the same time. They had a mean age calculated at the time of assessment of the NPI of 75.40 (SD=7.76). Considering all instances, there were seventy-five females and sixty-five males, with a mean education of 15.82 (SD=2.82). Participants included at each instance had AD dementia (n=108), or MCI due to AD (n=32), according to ADNI's inclusion criteria. Those in the AD dementia group

presented with CDR of 0.5 or 1, and MMSE between 20 and 26. MCI participants had a CDR of 0.5 and MMSE between 24 and 30. MCI participants were excluded if they later developed other syndromes (e.g., dementia with Lewy Bodies, Parkinson's disease).

Controls were selected as all participants who had AD dementia (n=573), or MCI due to AD (n=1838), who did not present with any psychotic symptoms at that timepoint; 1017 were females and 1394 males; they had a mean age at the time of NPI assessment of 74.58 (SD=7.81), and mean education of 16.06 (SD=2.65). The training set (a subsample of the dataset used for model fitting) was balanced by randomly sampling from the control group to match the same number as the psychosis positive group. This procedure was repeated 100 times, with different random seeds to account for variability and to obtain robust estimates of the model's performance, while the held-out test sets remained unbalanced to reflect the original sample distribution and to better reflect real-world testing (see section on statistical analytic procedure for further details).

7.3.3. Neuropsychiatric Inventory

The neuropsychiatric inventory (Cummings et al., 1994) has been previously described in other chapters of this thesis. In this study, participants were included if they had positive scores to the question relating to delusions, hallucinations, or both. The total scores of all the other neuropsychiatric symptoms were used as predictors; these have a score of 0 (indicating the absence of the symptoms) to 12 (excludes scoring options of 5, 7, 10 and 11, as the score is a product of frequency and severity which range respectively 0-4 and 0-3).

7.3.4. Brain metrics derived from processing with FreeSurfer

According to the ADNI protocols, T1 weighted MRI scans were acquired and processed using the FreeSurfer software, providing measures of cortical thickness, surface area and volume, and subcortical volume, that were then used as predictors, similarly to chapter 4. In this study, data was derived from the cross-sectional processing pipeline; the FreeSurfer versions used were 5.1, 6.0 and 7.0, based on the ADNI protocol employed. Where data was available from the most recent version, 7.0, this was employed; in the instances where this was not available, data from versions 6.0 was

used and if that was unavailable, data from version 5.1 was used. The variables used included were those common across FreeSurfer versions.

7.3.5. The Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS-COG-13 (Mohs, 1994), as outlined in chapter 6, is a test of cognitive function, scored in terms of errors. The version used in this study is composed of thirteen items with the following ranges: Q1. Word Recall (0-10), Q2. Commands (0-3), Q3. Constructional Praxis (0-4), Q4. Delayed Word Recall (0-10), Q5. Naming Objects and Fingers (0-5), Q6. Ideational Praxis (0-5), Q7. Orientation (0-8), Q8. Word Recognition (0-12), Q9. Remembering Test Instructions (0-5), Q10. Comprehension of Spoken Language (0-4), Q11. Word-finding Difficulty (0-4), Q12. Language (0-5), Q13. Number Cancellation (0-5). The individual subtest scores were employed as predictors in order to assess the value of each cognitive function tested.

7.3.6. ADNI Neuropsychological Battery

The neuropsychological battery of tests that is available via ADNI, as outlined in chapter 6, was used to select the same additional predictive features: the Clock drawing and Clock copying tests (0-5, higher scores reflective of better performance); the Category Fluency – Animals (the score reflects the numbers of animals recollected); the Trail Making Tests - A and B (the scores reflective of the seconds employed to complete the tests); the Rey Auditory Verbal Learning Test and Rey Auditory Verbal Learning Test - Delayed (0-15, higher scores reflective of better performance).

7.3.7. Statistical analysis procedure

For the analyses, a dataset was created by merging all ADNI tables containing the predictors mentioned above (see Appendix E for a full list of ADNI codes and corresponding labels), in addition to demographic and diagnosis-related information, which allowed selection of the pool of participants. The outcome variable consisted of the presence vs absence of at least one psychotic symptom.

The analysis script was created ad hoc, and it was implemented in Python, version Python 3.10.13 (*Python (version 3.10.13)*, 2023), using Spyder (version: 5.3.3) (Raybaut, 2022). Data processing was performed using the Python packages pandas and NumPy. For modelling, scikit-learn was used (including tools such as RandomForestClassifier,

train_test_split, cross_val_score, StratifiedKFold, accuracy_score, confusion_matrix, ConfusionMatrixDisplay, LabelEncoder, and DecisionTreeClassifier and export_graphviz for tree visualisation). Data visualisation was performed using graphviz, matplotlib and seaborn. Further details on the packages and versions, as well as the analysis scripts that were developed are provided here (OSF Folder).

Random Forest (Breiman, 2001) analysis creates multiple subsets of the original dataset, and it generates decision trees, each trained on a different subset; this helps in reducing variance and preventing overfitting (Yarkoni & Westfall, 2017), which is particularly important in datasets like the one created for this study, which includes a high number of predictors. The steps of the analysis were as follows.

1. Handling of missing data: The dataset had some missing data, particularly in relation to the neuropsychological variables: the overall missingness across all predictor variables was 0.18%, while percentage of rows missing at least one score was 0.07% (194 out of a total sample of 2551), with the score on the Trail Making Test part B presenting with the highest number of rows with missing data (n=129), followed by the Rey Auditory Verbal Learning Test – Delayed and the Trail Making Test part A (respectively missing n=39 and n=38); among brain areas, the highest number of rows missing the measure of a region was 13. For this reason, prior to running the Random Forest code, three imputation methods were evaluated, among which missForest (Stekhoven & Bühlmann, 2011) was the best performing one for this type of data, according to the metrics of Average Sum of Absolute Differences (SAD) and Mean Absolute Error (MAE) (Appendix E). This method is based on Random Forest: for each variable missForest fits a random forest on the observed part and then predicts the missing part; this is done iteratively for a set number of times. This method has also been shown to be particularly effective in scenarios such as ours, with multivariate data consisting of continuous and categorical variables, and in a dataset where the number of variables exceeds the number of observations. Therefore, missing values were imputed using an adaptation for python of the missForest algorithm, set at 10 iterations and 100 estimators (decision trees).
2. Reproducibility, selection of predictors and target variable: to ensure reproducibility, all random number generators were seeded (random seed 42);

furthermore, serial execution was selected to exclude minor nondeterminism of parallel execution. Columns from the previously missForest-imputed dataset were then defined as the demographic, neuropsychological, neuropsychiatric and neuroanatomical predictors (Appendix E), while psychosis (presence vs absence) was the dependent variable; the estimated total intracranial volume available from the FreeSurfer dictionary (ST10CV) was used for ROI normalisation: to account for head size variability, the structural measures of surface area and volume, and subcortical volume were normalised by dividing the raw value by total intracranial volume (TIV), yielding relative regional values; cortical thickness values were retained raw, as unlike surface area and volume, these are not correlated with TIV (Barnes et al., 2010; Schwarz et al., 2016). Therefore, the normalised metrics for surface area and volume, and subcortical volume, alongside the raw metrics for thickness were used for the analyses (Westman et al., 2013).

3. Random sampling and model training: For 100 independent repetitions data was stratified into an 80/20 train/test split, down-sampled the training partition to have equal class sizes (to address class imbalance) and trained a Random Forest with a maximum depth of 15, and 444 estimators (decision trees) on the balanced training data. As an internal estimate, 5-fold CV accuracy was computed on the balanced training set (James et al., 2023). For each repetition the full balanced training set was then refit, and evaluated on the held-out test set (20% of the data not used for training), to ensure evaluation on unseen samples (as opposed to the training sets, which were used to fit the models). Accuracy, sensitivity and specificity, and confusion matrices were computed for each repetition, and then averaged the metrics over the 100 repetitions (Fawcett, 2006).
4. Feature selection: cumulative importance was computed through the Mean Decrease in Impurity (MDI) method (Breiman et al., 1984; Friedman, 2001), averaged across the 100 forests, which ranks features in descending order and calculating the cumulative sum of their importances across all generated trees. MDI is based on the concept that at each split in each tree, the improvement in the split-criterion is the importance measure attributed to the splitting variable and is accumulated over all the trees in the forest separately for each variable.

Following previous work on importance-based feature selection (Guyon & Elisseeff, 2003; Louppe et al., 2013), a threshold of 70% cumulative importance was used to identify the most influential features. To assess robustness and select a parsimonious feature subset a set of additional processing steps were performed. An additional 5-fold outer CV procedure was performed: training folds were down-sampled to balance classes, random forest models were fit to these, features ranked by importance, and models evaluated using the top-k (highest-ranking variables) on the corresponding outer test fold. The optimal k (number of variables) was chosen as the value giving the highest mean outer-fold accuracy. A consensus list of top-k features across folds was assembled, and stability was assessed using pairwise Jaccard indices (Łukaszuk & Krawczuk, 2024) and by tallying feature occurrence across 100 balanced forests. Lastly, the union of top features was calculated based on top-k MDI importance ranking and outer-CV stability-selected features consensus.

5. Visual depiction of decision tree: a surrogate model tree (with a maximum depth of 5), based on the union of top features, was built to aid interpretability, as a representation of the behaviour of the forest (Molnar, 2020).
6. Directionality: as an additional explanatory step, a logistic regression analysis was subsequently performed (Appendix E) with the variables derived from the top union features, and psychosis as dependent variable, to indicate the direction of the relationship between predictors and psychosis.

7.4. Results

Random Forest Classification with 5-fold internal cross validation was employed to investigate how the different variables interact to predict the presence of psychotic symptoms, and which of those variables hold greater importance.

7.4.1. Model performance

The models demonstrate strong performance in using the selected features to predict psychosis, as shown by the average cross-validation scores, cross-validation accuracy, and the test set accuracy, sensitivity and specificity values (Table 7.2) (Sokolova & Lapalme, 2009). These results are further supported by the averaged, row-normalised confusion matrices, which indicate the proportion of correctly and incorrectly classified

cases within each true class (Figure 7.1). In Appendix E is the average confusion matrix based on counts of true and predicted classes across all iterations, which demonstrates the class imbalance between psychosis and non-psychosis groups.

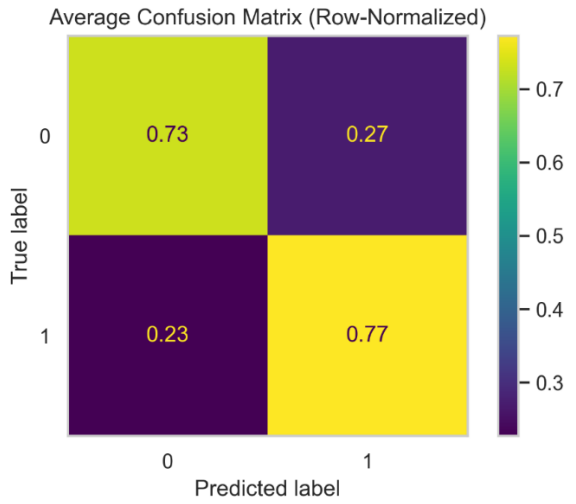
Table 7.2

Average performance metrics

Metric	**Value** (at 3 decimal points)
Average cross-validation accuracy, *M(SD)*:	0.746 (0.005)
Average test set accuracy:	0.733
Average sensitivity:	0.772
Average specificity:	0.731

Figure 7.1

Average Confusion Matrix



Notes. Confusion matrices are computed on the held-out test set for each of 100 Random Forest iterations and then averaged element-wise. The resulting matrix was row-normalised so that each row represents the fraction of cases within the corresponding true class predicted as psychosis or non-psychosis, providing per-class performance metrics (sensitivity and specificity) while accounting for variability across iterations.

7.4.2. Model interpretability

Two independent approaches were used to illustrate the most relevant features within the models. First, a feature importance ranking was plotted, based on the Mean Decrease of Impurity (MDI) method, to illustrate the highest-ranking variables contributing to 70% of cumulative importance; this generated 152 variables (Appendix E). To identify the optimal subset of features, outer cross-validation analysis of model accuracy was performed, showing performance plateau with optimal number of features (Appendix E). Based on this, the top twenty-six features were selected (and illustrated in Figure 7.2), as these were deemed enough to capture the majority of predictive power. Then, a second approach based on stability of the highest-ranking features was assessed, identifying features that consistently appeared among the top predictors across folds and repeated runs, which generated 66 features, appearing among the top twenty-six across five independent random forest models; from these, only the most stable features that appeared at least in two out of the five runs (n=25) were retained, as illustrated in Figure 7.3 (which shows the proportion of their appearance, ranging from two to five). Lastly, the union of features identified by both approaches is shown in Figure 7.4. This method selects the features retained in the optimised top twenty-six subset from the MDI analysis and stability-selected set (occurrences greater than 2), removing duplicates, thereby highlighting predictors that were prioritised by both methods. When comparing the feature sets to generate the union plot, all neuropsychological (n=9) and neuropsychiatric (n=5) features were found to be common, as well as four brain region metrics, while each method also contributed additional brain area metrics of interest not selected by the other, yielding a total of thirty-two features.

The set of top union features were employed to train the surrogate decision tree, providing a visual approximation of the Random Forest's decision rules (Figure 7.5). Although not providing the same level of predictive power as when the larger predictor set is used with the RF modelling, this tree is representative (Molnar, 2020) and shows how the complex interaction among the neuropsychological, neuropsychiatric and neuroanatomical variables combines to predict the likelihood of presenting with psychotic symptoms. While splits prioritize features with greater impurity reduction potential, which in this dataset are neuropsychiatric and neuropsychological scores,

neuroanatomical features tend to contribute more at later stages (Breiman, 2001). Performance metrics of the tree are reported in Table 7.3.

7.4.3. Feature importance

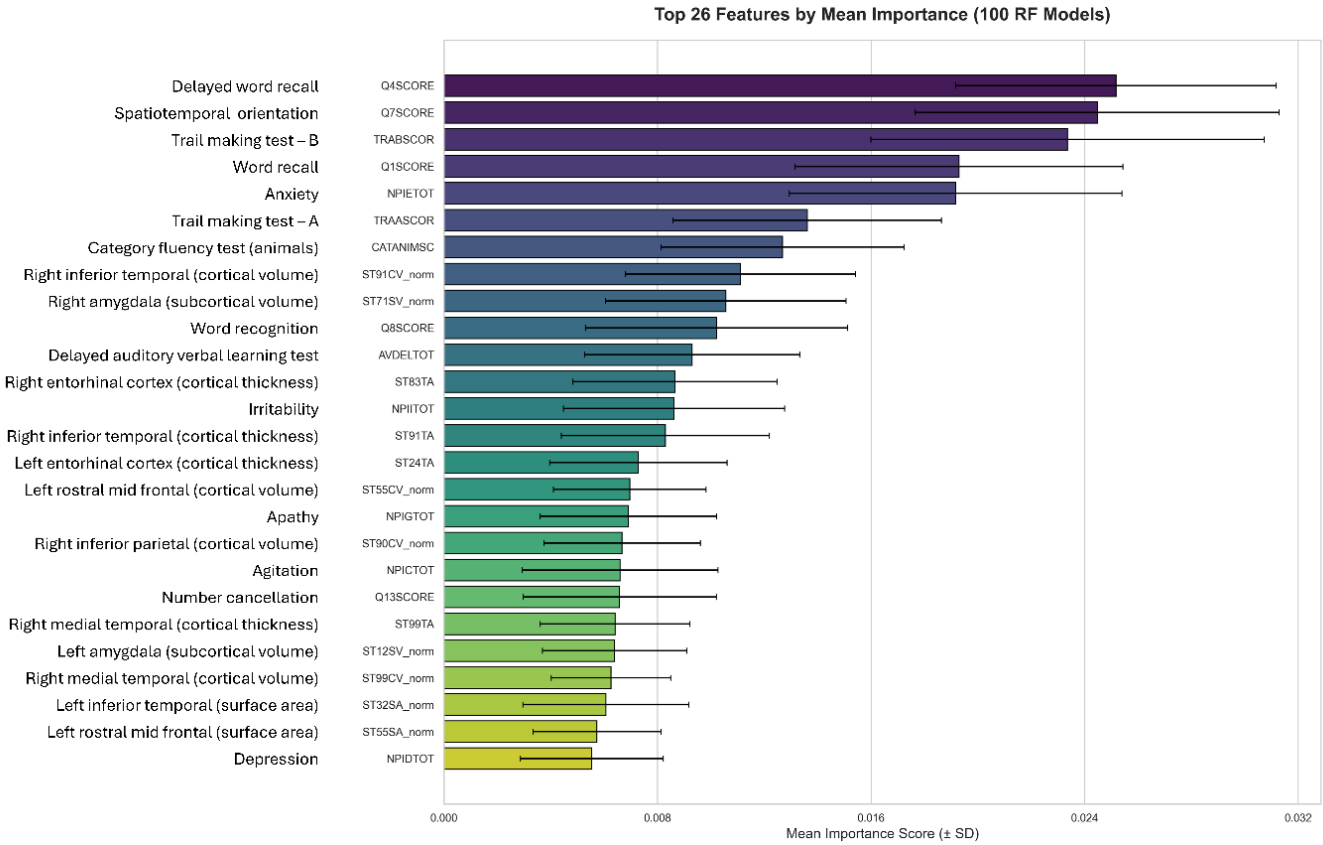
The five highest-ranking features from the union plot, which are consistently among the top predictors in the stability analysis, are four neuropsychological features, namely three items of the ADAS-Cog-13, corresponding to delayed word recall (Q4), spatiotemporal orientation (Q7), part B of the Trail Making Test, and word recall (Q1), and the neuropsychiatric symptom of anxiety.

Still holding great importance as shown in all three plots are the part A of the Trail Making Test, the category fluency test, the delayed auditory verbal learning test, and the number cancellation of the ADAS-Cog-13 (Q13), as well as four other items of the neuropsychiatric inventory, corresponding to irritability, apathy, agitation and depression.

Among brain regions, the highest-ranking in all plots related to the right inferior temporal and right amygdala, as well as the left entorhinal and right medial temporal. The MDI also uniquely identified the right entorhinal, the left rostral mid frontal, right inferior parietal, left amygdala and left inferior temporal; the stability analysis on the other hand contributed areas such as the left caudal mid frontal and left superior frontal, right accumbens, left mid temporal, left hippocampus, and right banks of the superior temporal sulcus.

Figure 7.2

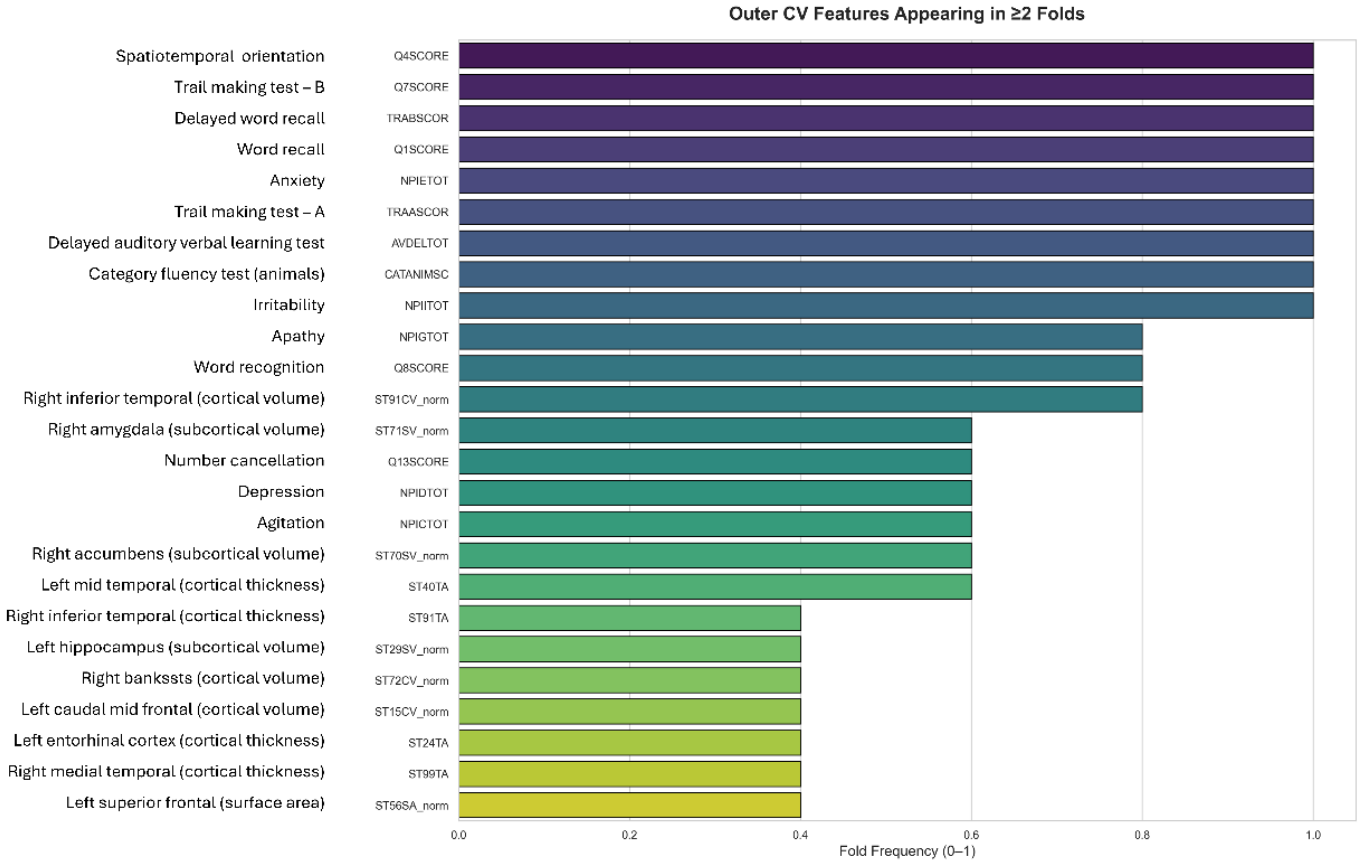
CV-selected MDI top 26 features



Notes. Features are ranked by mean importance, with horizontal bars representing the average importance and error bars indicating variability (±1 standard deviation).

Figure 7.3

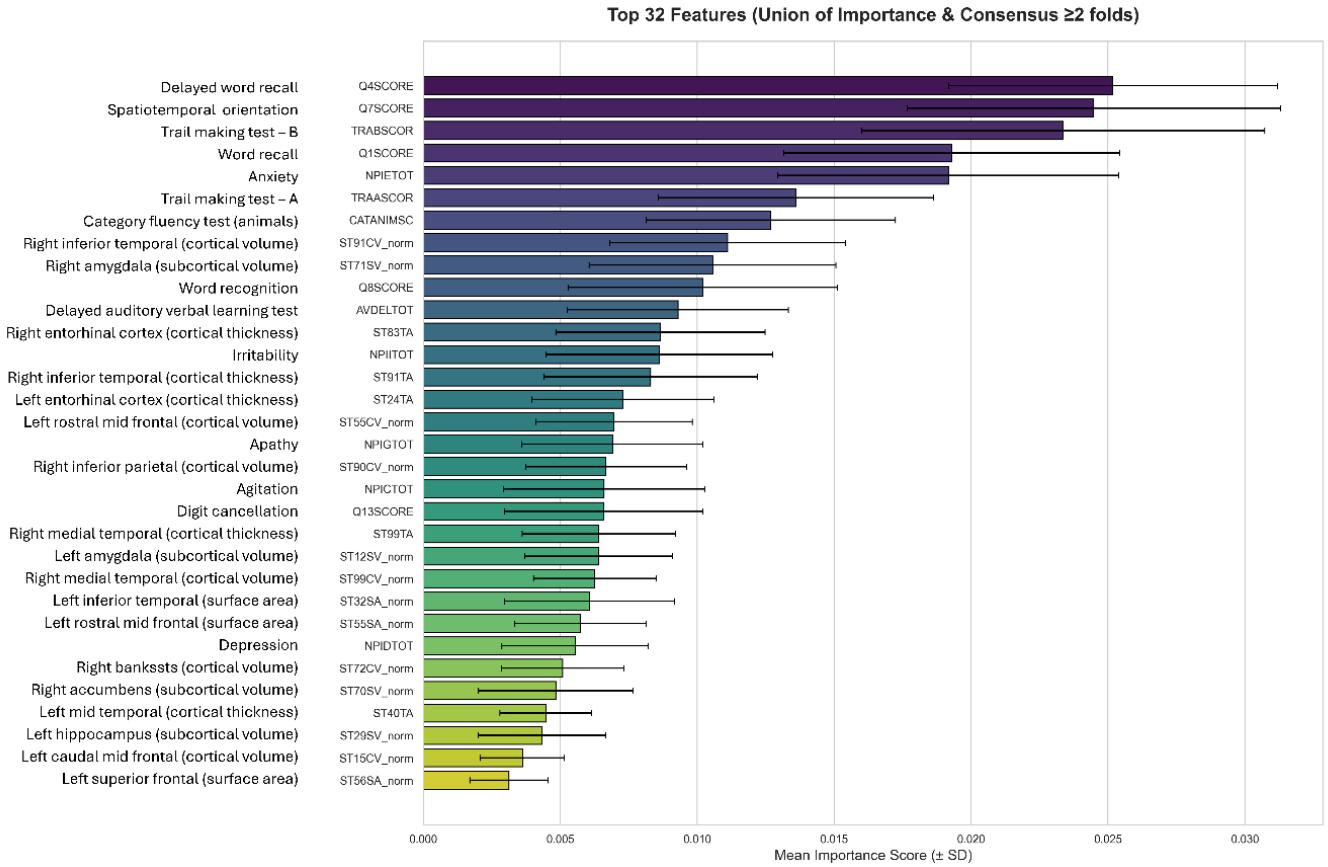
Outer CV-stability-selected 25 features



Notes. Fold frequency represents the proportion of resampling folds in which the feature was selected among the top-26. It ranges from 0 to 1, higher values indicative of more stable features; features were included if they featured at least twice across the 5 runs.

Figure 7.4

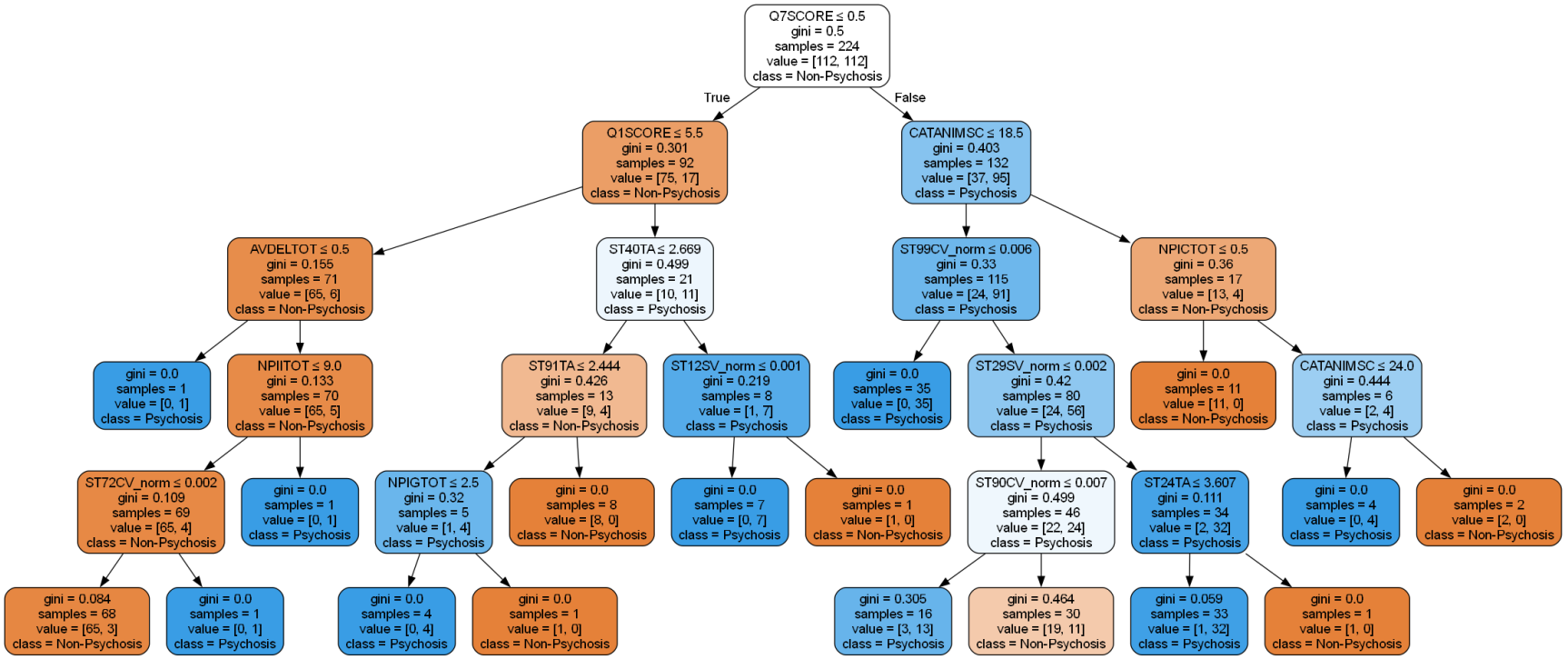
Union of selected top 32 features



Notes. Features are ranked by mean importance, with horizontal bars representing the average importance and error bars indicating variability (±1 standard deviation).

Figure 7.5

Surrogate decision tree



Notes. A surrogate decision tree is illustrated in the figure. This shows the criteria underpinning the decisions and the number of samples that are classified as having or not having psychosis. Each node contains the variable name along with the criteria applied, the Gini impurity value, the number of samples within the node, the value (in which cases of no psychosis, cases of psychosis are listed), and the predicted class at the node. While splits prioritize features

with greater impurity reduction potential, which in this dataset are neuropsychiatric and neuropsychological scores, neuroanatomical features tend to contribute more at later stages. For the ADAS-Cog-13 (variables Q7SCORE, Q1SCORE) higher scores indicate worse performance. In this example, the starting sample contains 224 participants (112 with psychosis and 112 without). The first split is based on the Q7SCORE score, which corresponds to spatiotemporal orientation); higher scores on this item (indicative of worse performance, in this case higher than 0.5) lead to the right side of the tree, where additional decisions are made to classify psychosis, based on the available variables (neuropsychological, neuropsychiatric and neuroanatomical). For instance, after the initial split, a lower score on the category fluency (CATANIMSC, in this case with a score lower than 18.5), leads to the left-hand side (left always indicative of that condition being true), where greater atrophy in the right medial temporal (ST99CV) is indicative of psychosis (with all 35 samples at that node fitting that classification). Alternatively, a subset of participants who have less impairment of the right medial temporal (ST99CV), the left hippocampus (ST29SV), but greater atrophy in the left entorhinal cortex (ST24TA) are predicted to have psychosis (with 32/33 samples at that node actually having psychosis). As a further example of a decision path, this time leading to a classification of non-psychosis, following the left-hand side of the tree, in a subset of participants who have lower scores on the orientation item (Q7SCORE) and word recall (Q1SCORE) of the ADAS-Cog-13 (indicating better performance), higher scores on the delayed recall on the auditory verbal learning test (AVDELTOT), less irritability (NPIITOT), but lower volume in the right banks of the superior temporal sulcus are predicted to not have psychosis (with 65/68 cases not actually having psychosis).

Table 7.3

Average performance metrics of surrogate tree

Metric	**Value** (at 3 decimal points)
Cross-validation accuracy, *M(SD)*:	0.728 (0.038)
Surrogate tree test set accuracy:	0.765
Average sensitivity:	0.607
Average specificity:	0.777

7.5. Discussion

To the author's knowledge, this is the first study that applies the Random Forest method of machine learning to the study of psychotic symptoms in Alzheimer's disease dementia and mild cognitive impairment. The goal was to create Random Forest models within which the combined impact of a range of different multimodal variables could be studied to predict the presence of psychotic symptoms. Compared to other methods (e.g., regression, as seen in chapters 4 and 6), Random Forest has allowed to produce a comprehensive model, able to investigate the impact of several complexly inter-related variables. The average metrics of the models demonstrated good performance (James et al., 2023; Sokolova & Lapalme, 2009), suggesting that this machine learning method can be considered a useful tool in the context of healthcare, to help to interpret clinical data (Javeed et al., 2023; Kumar et al., 2021).

In addition to the study of the predictive ability of the modelling, part of the aim was to identify the multimodal features which show greater discriminatory potential. In fact, in the context of neuropsychiatric symptoms such as psychosis, it is paramount to be able to identify which underlying features can predispose people to present these within the clinical picture of AD, in order to achieve more effective assessment and treatment plans. While these mechanisms can be investigated from a single viewpoint, considering for instance neuroanatomical or neuropsychological correlations in isolation (as was done in chapters 4 and 6 of this thesis), it was also hypothesised that, given the considerable heterogeneity between individuals, it is important to be able to consider how these variables may interact with each other. This approach provides an alternative to association-based studies with a predictive model which accounts for the importance of all potentially relevant features. Below, an interpretation of the variables which in this model provided greater contribution is outlined.

7.5.1. Neuropsychological predictive features

Among cognitive features, the ones that appeared as the most important and stable in this model, were mostly measures relating to episodic and working memory, through the subtests of the ADAS-Cog 13 of word recall (immediate and delayed), word recognition and spatiotemporal orientation, as well as the delayed part of the Rey auditory verbal learning test. This finds vast support in the literature mostly in relation to delusions

(Sultzer et al., 2014), the reason for which might be underpinned by the difficulty to inhibit the encoding of irrelevant information (El Haj et al., 2015; El Haj et al., 2018), paired with the failure to assimilate the correct information and to consider alternative possibilities (Sultzer et al., 2014), which could be linked to the maintenance of rigidly held beliefs over time (Ting et al., 2015).

Of relevance were also the Trail Making Test (part B more markedly than part A), which are normally considered measures of processing speed, task switching and overall executive function (MacPherson et al., 2017) as well as visual ability (Sánchez-Cubillo et al., 2009); the fluency test (based on the category "animals"), which has been linked to semantic memory, as well as executive function and verbal ability (Shao et al., 2014); the number cancellation subtest of the ADAS-Cog 13, again related to executive and visual functioning, as well as attention (Park et al., 2012). All the above aspects have been linked to psychosis in AD by association studies (e.g., lower performance on the trail making test part A (Paulsen, Salmon, et al., 2000) and B Impaired executive function has been linked to frontal (D'Onofrio et al., 2018) as well as temporoparietal (Ossenkoppele et al., 2015) areas, and its relevance within AD has led to the proposition of a "behavioural/dysexecutive variant" (Ossenkoppele et al., 2015) which appears evident also at early stages of disease. The investigation of psychotic symptoms in the presence of executive dysfunction, as well as greater atrophy in specific brain areas, as will be discussed below, warrants further exploration.

7.5.2. Neuropsychiatric predictive features

Among neuropsychiatric symptoms, anxiety emerged as the best predictor. Interestingly, depression, which is typically highly correlated both with anxiety, within an affective component (Antonsdottir et al., 2024), was not as highly ranked in this modelling, though it was still present within the top union features. An intricate relationship between affective and psychotic symptoms in AD has been suggested by previous studies, which propose a genetic relation in a joint affective-psychotic phenotype of AD (Antonsdottir et al., 2024). Importantly, an association was suggested in MCI as well (Liew, 2019), which resonates in this study's sample inclusive of participants with a diagnosis of MCI due to AD. Particularly relating to anxiety, which was registered consistently in the stability analysis, it has been suggested that this symptom in AD might be related to attentional focus to socioemotional stimuli that could be

perceived as potentially threatening, as well as socioemotional difficulties, which may go unrecognized due to the challenges in communicating them (Mendez, 2021). This might be particularly relevant in the presence of psychotic symptoms, where the struggles to communicate the experience (El Haj et al., 2017), and the perceived threat are heightened by the increased sensitivity to perceive emotional pain and emotions that have a negative connotation (Nakatsuka et al., 2013). Furthermore, a previously proposed model that considers the multiplicity of mechanisms interacting to contribute to hallucinatory experiences (El Haj et al., 2017), has suggested that psychological distress, under which anxiety can be considered as a negative emotional state, might function as a potential trigger in people who already present with underlying predisposing variables, highlighting the importance of models that incorporate different types of predictors.

Both hyperactivity-related symptoms, agitation and irritability, were identified as important predictors in the models, with irritability ranking highest. While they constitute two distinct dimensions, agitation and irritability typically co-occur in AD (Hiu et al., 2022) and MCI (De Vito, Calamia, Weitzner, & Bernstein, 2018), and it has been suggested that these might be inter-related with psychotic and affective dimensions (Koenig et al., 2016). Processes that were suggested to underpin anxiety and psychotic symptoms, such as heightened threat perception and impaired emotion regulation, have been proposed in relation to the presence of agitation and irritability as well (Leibenluft & Stoddard, 2013; Rosenberg et al., 2015). This might point in the direction of a common psycho-social explanation which might lead to the co-occurring presence of this clinical presentation. As seen in chapter 2, different associations were identified in relation to disease severity; particularly, the neuropsychiatric clinical picture became more intricate with disease advancement, with overlapping psychotic, affective and hyperactive symptoms, which constituted distinct syndromes at earlier stages.

Lastly, the neuropsychiatric symptom of apathy has appeared among the top features; apathy is a is a complex multi-dimensional syndrome, and it has been suggested that almost up to 90% of individuals with Alzheimer's disease experience it (Zhao et al., 2016), it presents however many commonalities of clinical presentation with depression to the point of having partially overlapping diagnostic criteria. The presence of both symptoms in a predictive model of psychosis requires additional clarification.

7.5.3. Neuroanatomical predictive features

An influence of cognitive measures that assess executive function, as well as episodic memory, in a predictive model of psychosis, appears particularly relevant when considered together with contribution of greater atrophy in areas such as frontal, temporal and parietal regions, as identified by this model (Uysal, 2023). These areas have been identified in studies on brain correlates of different manifestations of psychotic symptoms in AD, in relation to the failure to integrate new evidence and monitor existing beliefs (Castelluccio et al., 2020), as well as an increased sensitivity to perceive emotional pain and emotions that have a negative connotation (Nakatsuka et al., 2013), and the suggestion is that their inter-related contribution might impact the overall predictive ability of this model.

Particularly the entorhinal cortex, which featured highly in this model, is involved in the perceptual processing of stimuli, in novelty detection, associative learning, and processing episodic, recognition, and autobiographical memory (Prasad et al., 2004), as well as inhibition and attentional control (Hampshire et al., 2010). Recent studies (D'Antonio et al., 2019; J. Lee et al., 2021) have found greater atrophy in the entorhinal cortex in association with psychotic symptoms, while controlling for disease severity. It would appear that this region, importantly linked with processes related to episodic memory and executive function, is an important area to consider in discriminating AD with and without psychosis.

A further area of interest appearing to hold great importance in this model, which contrastingly, as yet, has produced limited results in region of interest studies, was the amygdala. The amygdala is a brain region that has been repeatedly linked to emotional processing, especially that of fear and anxiety (Mavrych et al., 2025), with dysfunction noted within AD (Chen et al., 2021). In one previous study on different subtypes of delusions (Nakatsuka et al., 2013), dysfunction of the right amygdala was found to relate to the delusion of not being at home, and the same delusions also showed correlation with a measure of anxiety and phobia. Considered the importance that anxiety held in this model, it could be suggested that impaired ability in processing anxiety might be conducive to the experience of symptoms of psychosis, and to the difficulty to correctly interpret reality.

7.5.4. Limitations

This study presents with a few limitations that are important to consider. The first relates to the way in which variables are selected in Random Forest: in decision tree models, variables that provide the greatest reduction in impurity are prioritized for early splits. In this dataset, cognitive test results and neuropsychiatric scores tend to appear higher in the tree structure (and lead to earlier splits) compared to neuroanatomical features, which on the other hand carry greater variability and noise due to individual brain differences and imaging conditions (that likely remain despite the ROI normalisation procedure implemented). This is to be accounted for when interpreting the contribution of variables, as clinical features typically yield purer splits, while brain structural features are often relegated to later branches, where finer subgroup differentiation occurs (Breiman, 2001). Furthermore, although two independent approaches were employed to identify features, biases derived from feature importance methods should still be considered (Genuer et al., 2010; Strobl et al., 2007). Specifically, it is likely that due to the high number of brain areas included in the model, which are likely highly inter-correlated, their individual importance could have been diluted, thus resulting in an overestimation of the neuropsychological and neuropsychiatric components, and fewer neuroanatomical ones. Despite the cross-validation analysis of model accuracy showed a plateau at about twenty-six features, it is highly probable that further contribution from additional brain areas might be contributing to the overall accuracy of the model. Future studies might consider aggregating features at the level of anatomical or functional brain networks; such approach could have the potential to both reduce collinearity among single brain regions, and enhance interpretability by linking machine learning results to established brain systems and behaviour (Li et al., 2024).

Similarly to what outlined in previous chapters (e.g., 4) choices were made in the design of the study, to maximise the study sample, which constitute potential limitations and should be addressed in future investigations. First, it was not possible to stratify for disease severity, as participants who were diagnosed with either AD or MCI due to AD were included. Furthermore, in this study rather than selecting a specific time-point from the ADNI dataset, participants who were at different stages of the disease were pooled together. Lastly, for the same reason of maximising sample size, here it was decided to include participants who presented with either delusions or hallucinations;

while this is considered a valid approach as discussed in previous chapters of this thesis, future plans should consider the specific mechanisms relating to each manifestation (Fischer, 2020) .

Other limitations pertaining to the ADNI dataset have been previously highlighted in the limitations' sections of chapters 2, 4 and 6 of this thesis, however it is particularly important in the context of training AI models to reflect on the lack of generalisability of the ADNI database. As seen in previous chapters, ADNI's participants are mostly white, highly educated people coming from higher socioeconomic backgrounds: particularly when considering the possibility to predict neuropsychiatric symptoms, such as psychosis, which can present differently across different ethnic groups and cultures, it would be highly beneficial to replicate these analyses in more representative and inclusive database, in order to overcome the potential risk of bias.

7.6. Conclusions and future directions

In conclusion, for the first time, this study employed Random Forest modelling, based on a combination of neuroanatomical, neuropsychological and neuropsychiatric features to predict, with good accuracy, the likelihood of participants with MCI and AD presenting with psychotic symptoms. In agreement with the literature (El Haj et al., 2017), the complex interaction among features is proposed as contributor to psychosis in AD. Random Forest as a machine learning method has started to gain popularity for use with clinical datasets, however prior to this investigation, it had not previously been used to explore the value of underlying mechanisms of psychotic symptoms. It would be useful to perform further investigations, to validate the modelling in larger datasets, which would provide with the opportunity of stratifying according to disease stage and severity, to explore the features that link to different manifestations of psychotic phenomena, and to test the potential of further methods of selecting brain areas to assess their importance at a network-based level.

Chapter 8 – Study 5: Development of a new digital monitoring tool for behavioural symptoms of dementia

8.1. Overview

In the previous chapters the underlying mechanisms of psychotic symptoms have been investigated using different approaches. One point that was made evident is the importance of the assessment and classification of psychotic and other neuropsychiatric symptoms. Currently available instruments, as seen in previous chapters, largely consist of interviews administered by a clinician to an informant (typically an informal caregiver such as spouse or relative) who are asked to reflect on past occurrences of the symptoms over a period of time such as the previous four weeks, and as such they present two main limitations: that of heavily relying on accurate recollection from informants on past occurrences, and of not allowing for a frequent capturing of these symptoms. Importantly, more detailed monitoring of symptoms is expected to provide more accurate outcome measures for association/prediction and intervention studies. To address this gap, and in line with objective 7 of this thesis, this study sought to design and implement a digital monitoring tool that can be completed directly by a caregiver, thus allowing for more frequent collection of data. This project consisted of a study divided into two components, for both of which participants were recruited using the digital platform "Join Dementia Research" (*Join Dementia Research*, n.d.). Component A (co-design), in which a group of four current and four former caregivers of people with dementia provided inputs on all aspects of the tool, such as feasibility, usefulness, ease of use, clarity of questions posed and of instructions for use, and wording of the questions. This was done in three phases: phase 1 consisted of interviews and small focus groups where all the above aspects were discussed; phase 2, carried out only with the participation of the current caregivers consisted of trialling the co-designed tool (complete with the implemented modifications based on the previous phase); phase 3, again only with the current caregivers, consisted of feedback collection through an interview and a survey. Component B (pilot) was a pilot trial of the tool, implemented in collaboration with eleven dyads of participants (one person with dementia and one caregiver). This again consisted of three phases: phase 1 was an in-person session of approximately 2 hours, in which the participants with dementia were asked to complete a neuropsychological battery of tests, while the caregivers were

asked to answer on the neuropsychiatric and functional status of the person with dementia, and were instructed on the use of the new digital monitoring tool; phase 2 consisted of trialling the tool for the duration of a month; phase 3 once again consisted of feedback collection through interviews and a survey, as well as the administration of the full Neuropsychiatric Inventory (NPI) to the caregiver to test the performance of the digital monitoring tool. In this chapter, both components of this study are illustrated, focusing on: the co-design elements and the feedback provided by all caregivers, the tool performance compared to current diagnostic standard and the potential benefits of this tool within the framework of personalised assessment.

8.2. Introduction

In chapter 1, the overarching aims of this thesis were introduced: the first was to explore the literature and propose new studies that advance the understanding of the mechanisms that might come into play to predispose certain individuals with AD to experience psychotic symptoms; the second one to propose a new tool which has the potential to improve their assessment. Chapters 2 to 7 have focused mostly on the first aim, while this chapter, presenting the last study of this thesis, addresses the second aim. Furthermore, the findings of the systematic reviews and studies presented in the previous chapters have additionally highlighted existing gaps in the literature, which are going to be explored in the following sections as rationale for the proposition of the novel digital tool. In chapter 2 it was shown how psychotic phenomena have a fluctuating, mostly increasing pattern over time and with the advancement of disease, frequently, but not always, clustering together, and particularly at later stages of disease, forming part of larger clusters inclusive of symptoms such as affect and hyperactivity. One argument that has been made as a result of the two systematic analyses and the two independent association studies, is that focusing research efforts on the specific psychotic phenomena (i.e., separating delusions from hallucinations, and also exploring the thematic components of paranoia and misidentification) has the potential to yield clearer results on the associated neuroanatomical and cognitive features. On the other hand, one potential issue to this approach is the available sample size, even in large datasets such as the one used in this thesis, which is the main reason why in the Random Forest study presented in the previous chapter, it was chosen not to perform further analyses on the subtypes, as the sample sizes would have been too small for an

accurate prediction study. This issue might be at least partially explained by the fact that the assessment of psychotic symptoms typically relies on informant recollections of symptoms experienced typically over the past month, and in large studies such as ADNI it is only collected once a year, thus it may be subject to underestimating biases (Stella et al., 2015). Therefore, in concomitance with the newly proposed criteria for psychotic symptoms (Cummings et al., 2020; Fischer, 2020), it appears important to consider the limitations of current assessment, particularly with respect to the possibility of a more frequent capturing of neuropsychiatric and behavioural symptoms. This could allow for a precision-based approach to the monitoring of these symptoms, producing more precise samples to be used in the studies which explore their underlying mechanisms, as well as potential details for management strategies. As mentioned above, current instruments (among which the most widely used is the NPI (Cummings et al., 1994), as seen in the reviews presented earlier in this thesis, and according to a recent systematic review on the topic by Pozzi et al. (2023)), collect information through an informant, who (for example, in the case of the NPI) reflects on the symptomology that has changed since disease onset, and has been experienced by the person typically within the past four weeks. It has been suggested, however, that there may be challenges associated with the accurate recognition and reporting of neuropsychiatric symptoms (Stella et al., 2015). These challenges may be related to aspects discussed in chapter 1, such as caregiver distress and burden associated with the presence of neuropsychiatric symptoms (Scerbe et al., 2023; Vespa et al., 2021), which may lead to under- or over-estimation of the symptoms (recall bias). Further elements which may hinder accurate recollection may include caregivers' age and cognitive status, as well as cultural beliefs (which might influence what is considered "normal", therefore underestimating potentially relevant symptoms), or denial of the symptoms (de Medeiros et al., 2010). Furthermore, as introduced in chapter 1, it has been suggested that an appropriate analysis of potential triggers associated with the presentation of the symptoms, which is currently not captured by the NPI, may be relevant to further understanding their occurrence, and aid the research into potential treatment strategies (Pozzi et al., 2023; Smith et al., 2020). A recent review of the currently available scales and tools for neuropsychiatric symptoms (NPS) in dementia (Pozzi et al., 2023) has proposed suggestions to improve current assessment. These include strategies to avoid caregiver recall bias features as one of the most important, alongside being short and easy to

understand and to use, including information on potential triggers and contextual factors, providing data to clinicians in a timely way thus promoting intervention-oriented approaches. Recent studies such as Morganti et al. (2018) and Cho et al. (2023) have addressed some of these points, proposing a paper-and-pencil, diary-based collection of neuropsychiatric symptoms, respectively from nursing home staff and informal caregivers, the latter also including a mapping of potential triggers. These studies' results suggest that a more frequent collection of data, that contextually looks at interrelated factors, has the potential to overcome the recall bias and thus advance the understanding of the key mechanisms of neuropsychiatric symptoms.

Based on these premises, it appears timely to propose new strategies for assessment and monitoring of neuropsychiatric symptoms, in order to capture in a more precise way the known symptomology. As seen in the previous section, a first goal would be that of collecting data more frequently, which would help understand how phenomenology of psychotic and other neuropsychiatric symptoms may occur on a daily basis, and whether this accurately maps to the data obtained using pre-existing instruments. Importantly, this would allow evaluation of whether more frequent and accurate measurements are associated more closely with certain other symptoms, such as other neuropsychiatric symptoms, cognitive symptoms, as well as associations with brain regions and networks. At the same time, it could provide a personalised profile of the experience of the symptoms, which could be used to inform more suitable management strategies. By moving on from paper-and-pencil tools, it is possible that a digitalised tool would provide further opportunities for customisation, as well as resulting quicker and easier to use (Pozzi et al., 2023). For these reasons, this study is intended to develop and trial a digital tool, in collaboration with caregivers of people with dementia, aimed at the daily monitoring of psychotic and other neuropsychiatric and behavioural symptoms.

8.2.1. Participants' involvement in research and personalised approach based on digital healthcare

As introduced in chapter 1, the research that involves participants with dementia has seen an exponential growth of Patient and Public Involvement and Engagement (PPIE) in the past three decades (Griffiths et al., 2024). PPIE refers to the notion that people who have lived experience of an area of health and social care should inform and shape research in that area. Research is therefore conducted "with" the participants rather

than “for” them (NHS Health Research Authority, 2026). This has the aim to improve the quality and meaningfulness of health and social care research, by focusing on the priority outcomes of people with lived experiences (Innovations in Dementia, 2023). Therefore, while conducting research that focuses on improving the lives of people with dementia, one of the main considerations prior to the beginning of this study was to develop a protocol which would allow collaboration with its primary intended users, thus encouraging people with lived experiences to become active “partners in research”, as outlined by the NHS Research Scotland (NHS Research Scotland, 2023). This was achieved by developing a protocol in which co-design processes were embedded throughout, firstly with the co-development of the tool and secondly with the collection and analysis of feedback which continuously informed later versions of the tool, as well as other aspects of the study. Co-design is closely related to PPIE, and it specifically refers to designing research that is built on the consideration of the experience and needs of users (Lord et al., 2022).

Another aspect that was greatly considered while developing this protocol was that of designing a project in which the participants’ neuropsychological and neuropsychiatric profile, and specific individual needs and circumstances (for example, deciding together which symptoms to monitor based on their experience and providing a space to note any further relevant information such as potential contextual triggers of the symptoms) would be taken into account. In order to achieve this, the potential of a precision medicine approach was explored: previous studies in dementia research have suggested that the direct involvement of participants in studies based on precision medicine brings about positive engagement and commitment over extended periods of time, particularly when it is aimed at early intervention for risk reduction (Isaacson et al., 2018). The concept of precision medicine is a relatively novel method of considering health issues such as Alzheimer’s disease with a focused and patient-specific approach (Arafah et al., 2023), taking into account individual heterogeneity in the environment, genetic profile, and lifestyle factors (Berkowitz et al., 2018). While this has been typically applied to the study of the role of genetic and epigenetic factors (e.g., Tripathi et al., 2024) or to the trial of new treatments (e.g., Toups et al., 2022), this project is based on the premise that such an approach can be useful in the study of neuropsychiatric and neuropsychological profile of people with dementia, and that collecting this type of data systematically and frequently can provide valuable information to create a personalised

type of assessment and thus potentially inform management strategies of these symptoms from a cognitive and behavioural perspective.

Recent studies (e.g., Granström et al., 2020; Kjörk et al., 2022) have shown how the implementation of digital tools in clinical practice are conducive of positively perceived, personalised strategies as they promote person-centred approaches and direct involvement of the patients in their care and engagement with health professionals. It is unsurprising given the digitalisation of healthcare (NHS Confederation, 2025) that in recent years the research into digital solutions to support and complement healthcare has seen a surge in publications (Sohn et al., 2023). Within the context of dementia, different aspects have been tackled, such as cognitive assessment tools (e.g., Rhodius-Meester et al., 2024); digital assistive tools (e.g., Köhler et al., 2024; Wichmann et al., 2021), physical activity monitors (e.g., Farina et al., 2019); "ambient intelligence" technologies to support with daily life activities (D'Onofrio et al., 2017); digital online programmes aimed at caregivers such as the World Health Organization course iSupport (World Health Organization, 2019), and other psychoeducation programmes (e.g., González-Fraile et al., 2021; Huang et al., 2025; Scerbe et al., 2023) and a digital assessment tool aimed at identifying caregivers unmet needs (Biernetzky et al., 2025). With respect to neuropsychiatric and behavioural symptoms, while a recent digitalisation of the Thai version of the NPI has recently been proposed (Rangseekajee et al., 2021), this was intended to digitally mirror the content and functionality of the NPI, with no expectation of frequent data collection (the application was only used once by the caregivers, with no continuous monitoring); furthermore, the app proposed by this group consisted of a cultural adaptation of the items of the NPI (thus translated with no further modification).

The current study sets out to provide a more comprehensive measure of the main symptoms of interest (psychotic symptoms), based on reviews of currently available instruments (including, but not limited to, the NPI), newly proposed criteria for psychosis in dementia (Cummings et al., 2020; Fischer, 2020), and known symptom phenomenology (e.g., in relation to thematic components) as investigated in previous chapters of this thesis. There is also no tool that exists today that is designed to monitor behavioural symptoms daily, while producing outputs that can be used by the person with dementia and their caregivers as an accurate way of monitoring the fluctuations of

such symptoms in a personalised manner, as this project intents to do. At the same time, a recent review has highlighted a lack of digital tools aimed at supporting caregivers mental health (Petrovic & Gaggioli, 2020): considered the burden that neuropsychiatric symptoms place on caregivers, as seen in previous chapters of this thesis, the importance of monitoring caregivers distress associated with these symptoms was considered, as well as providing an additional space at the end of the questions to provide additional comments.

Despite many successful projects as seen in the above sections, studies have also highlighted the importance of considering a potential barrier to participation that is constituted by the "digital divide", defined as a difficulty to access digital technology due to availability and skills, which can be linked to socio-demographic aspects that include age (Arighi et al., 2021; Cheng et al., 2020). In a qualitative study that looked at the main barriers to a positive reception of the digital transformation of the healthcare sector, which led to a failed uptake of the technology proposed, lack of or inadequate technological understanding and competence were highlighted as key factors (Iyanna et al., 2022). Lastly, a recent systematic review on the challenges in co-design of digital healthcare interventions (Duffy et al., 2025) has highlighted the role of collaboration and communication: user uptake may fail if the interests of the research team are not aligned with those of the users, and if there is no clarity on the key concepts of the proposed technology. One way in which these barriers to participation can be overcome is by creating and adopting digital tools that are suitable to the needs of the intended users, as well as providing comprehensive information within the research protocol to promote electronic health (eHealth) literacy (Neter & Brainin, 2012). Improving digital literacy and engaging with digital resources has the potential to foster a sense of empowerment (Cho et al., 2025), therefore studies such as the current one which aim to promote digital tools to be applied in the healthcare context need to consider these aspects and implement strategies to ensure positive engagement from the users. Similarly, one key aspect which might make the difference in terms of user engagement is the clarity of the language (Duffy et al., 2025): it was considered important to define and characterise neuropsychiatric symptoms, in a way that leaves no space for ambiguity. In a recent revision of the criteria for psychotic symptoms, it has been suggested that further definitions and examples of psychotic phenomena would be useful to ensure clarity and promote caregivers education on this area (Cummings et al., 2020). This concept has

been applied in this study and extended to all neuropsychiatric symptoms monitored, in order to promote clear communication between research team and service users.

8.2.2. Aims and objectives of the current study

Considered all these elements, a research protocol was developed which would consider the importance of a personalised approach to symptom monitoring, taking into account the priorities of the service users, in order to design a tool which would be appropriate and useful, and that by using novel and easily accessible technology, would have the potential of bridging a gap between the digitalisation of health and the need for person-centred care (Leplege et al., 2007).

The aim of this project is therefore to develop, assess the feasibility, and pilot a novel digital tool for the monitoring of behavioural symptoms in dementia, created on the basis of reviews of the phenomenology of psychotic symptoms in dementia. The tool was based on the newly proposed criteria for psychosis, on reviews of previous literature on the topic, and of the instruments currently used to assess psychotic symptoms in dementia. It is intended to optimally capture the key features of psychotic and other neuropsychiatric symptoms through daily collection, thus capturing symptom fluctuations, as well as frequency, intensity of the occurrence, and impact on both the participants with dementia and their caregivers. The project consisted of two components: a first, co-design component (A), aimed at working in collaboration with current and former caregivers of people with dementia, in order to develop together a tool which would be suitable, and address the desired functionality of this population; a second component (B), aimed at piloting the tool, as well as collecting neuropsychological and neuropsychiatric data, and assess the tool's performance compared to current diagnostic standard.

8.3. Methods

Ethical approval for this study was sought and obtained by the University of Strathclyde, University Ethics Committee

8.3.1. Participants and Recruitment

Participants were recruited using the digital platform "Join Dementia Research" (*Join Dementia Research*, n.d.), which is funded by the Department of Health (*Department of*

Health, n.d.) and delivered by the National Institute for Health and Care Research (*National Institute for Health and Care Research*, 2024) in partnership with Alzheimer Scotland (*Alzheimer Scotland*, 2026), Alzheimer's Research UK (*Alzheimer's Research UK*, 2026) and Alzheimer's Society (*Alzheimer's Society*, 2026). The two components of this study were advertised on the platform as follows.

1. Component A, "Co-design of digital monitoring tool for behavioural symptoms in Alzheimer's disease", was open from the 11th to the 27th of November 2023. The inclusion criteria consisted of being, or having been, the caregiver of a person formally diagnosed with dementia; being aged 18+; able to speak, read and understand the English language; free from visual impairment (once correction with glasses has been considered) that would affect use of the digital tool; free from any neurological/psychiatric conditions which affect cognition. Eight participants (caregivers) were recruited (Table 8.1), within Scotland's Central Belt.
2. Component B, "Pilot trial of a new digital monitoring tool for behavioural symptoms of dementia", was open from the 27th of November 2023 to the 30th of August 2024. The inclusion criteria consisted of having received a formal diagnosis of dementia, and being the caregiver of a person with a diagnosis of dementia; being aged 18+; able to speak, read and understand the English language; free from visual impairment (once correction with glasses has been considered) that would affect use of the digital tool; free from any neurological/psychiatric conditions which affect cognition. Twenty-two (eleven dyads) of participants (one caregiver and one person with dementia) were recruited (Table 8.1) within Scotland's Central Belt.

In both components of this study, volunteers who matched to the study based on inclusion criteria filtered by the platform (e.g., diagnosis, geographic) were first contacted via email, to enquire about their interest in the study, based on Join Dementia Research protocol for enrolment. Following a positive answer, contact was made via phone call to assess eligibility. All participants were sent the Participant Information Sheet, tailored per component and participant group (see Appendix F), summarising key information concerning their participation to the study. After this, if the volunteer agreed to participate, they were invited to the first meeting. During the first meeting (mostly held

in person with the exception of one focus group of Component A (co-design) which was held online) participants signed their consent forms (Appendix F) (the participants who attended the online meeting were sent their consent forms via post and they sent them back signed to the University of Strathclyde).

Characteristics of all the participants are outlined in Table 8.1, which reports the age, gender, education, type of dementia/cognitive impairment (as one participant presented with Mild Cognitive Impairment (MCI) rather than dementia), and the relationship between the person with dementia/MCI and their caregiver. The characteristics are reported grouped based on their participation in Components A (co-design) and B (pilot), and within these, the categories of current or former caregivers (Component A), with the latter participating only to the focus groups/interviews, and caregivers or participants with dementia/MCI (Component B). In Component A (co-design), the age of the caregivers ranged from 56 to 84, and their education counted in years ranged from 13 to 23. Their relation to the person with dementia was mostly of spouses and children, with one granddaughter and one son in law. In Component B (pilot), the caregivers' age ranged from 47 to 76, while that of people with dementia/MCI from 57 to 95; the education in years ranged respectively from 10 to 28, and from 10 to 23. In this case as well, the relations were mostly consisting of spouses and children, with two siblings and one personal assistant. All participants with dementia/MCI were retired, as well as their spouses. The other caregivers (siblings, children, son in law, granddaughter and personal assistant) were still in employment. As mentioned above, all participants were recruited within the Central Belt of Scotland. The majority resided in either Glasgow (n=7) or Edinburgh (n=7), with further three residing in the greater Glasgow area, one in Stirling, one in Dumfries and Galloway and one in the Borders. With respect to their ethnicity, they were all White (British).

Table 8.1

Characteristics of the participants included in the study

Characteristics	Component A (co-design)		Component B (pilot)	
	Current caregivers	Former caregivers	Caregivers	Participants with dementia/MCI
Number of participants	n = 4	n = 4	n = 11	n = 11
Age, *M(SD)*	66.50 (12.55)	69.00 (9.41)	63.45 (9.67)	73.09 (12.25)
Gender	Female = 4	Male = 2 Female = 2	Male = 3 Female = 8	Male = 7 Female = 4
Relationship	Spouse = 2 Daughter = 2	Spouse = 1 Daughter = 1 Son in law = 1 Grand -daughter = 1	Spouse = 6 Son = 2 Sibling = 2 Personal assistant = 1	-
Education, *M(SD)*	17.50 (4.20)	13.00 (2.44)	16.45 (4.25)	16.72 (5.31)
Type of cognitive impairment	-	-	-	1 MCI 3 Mild AD 2 Moderate AD 1 Severe AD 2 Moderate LBD 1 VD 1 Behavioural FTD
Additional health issues	-	-	-	6 Hearing problems 6 High bp 3 Mobility issues 2 Cholesterol/ diabetes 2 Stroke 1 Communication issues 1 Visual problems

Abbreviations. M = mean; SD = standard deviation; MCI = mild cognitive impairment; AD = Alzheimer's disease; LBD = Lewy Body dementia; VD = vascular dementia; FTD = frontotemporal dementia; bp = blood pressure.

8.3.2. Procedures

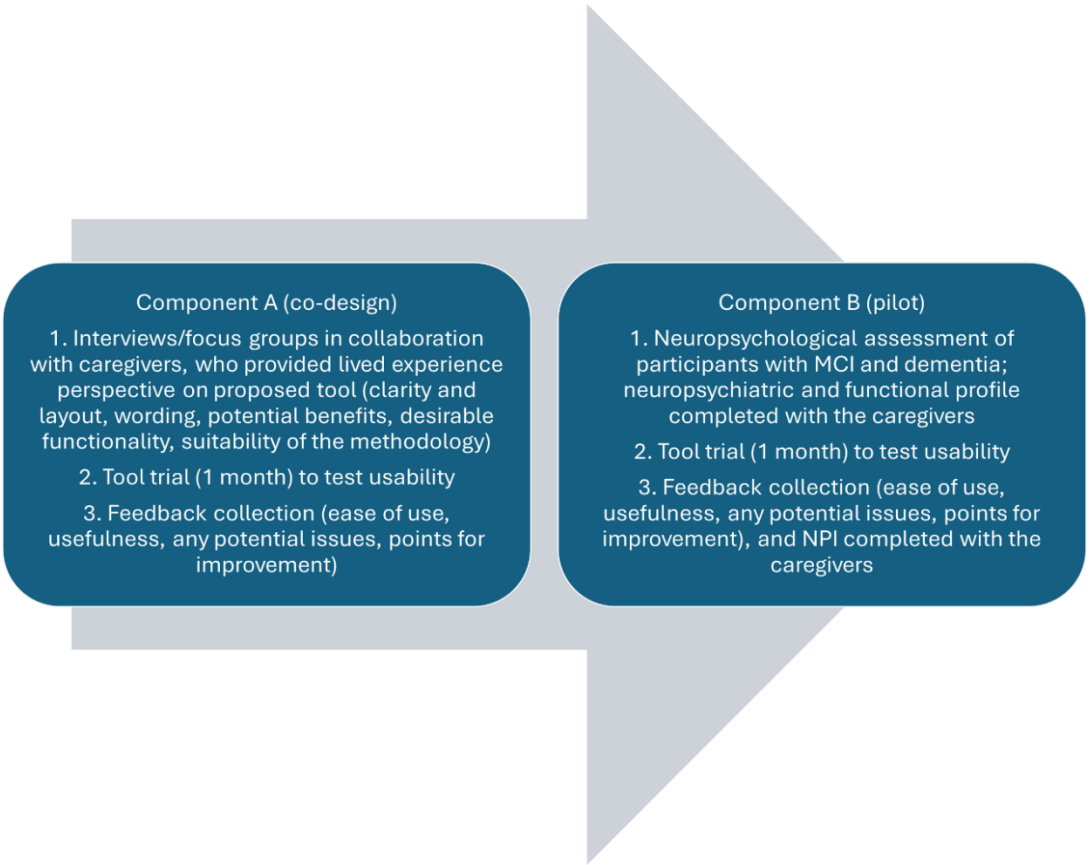
Figure 8.1 shows the procedures of the two components of the study. Prior to the beginning of the first study, a first draft of the digital monitoring tool was developed using Qualtrics (*Qualtrics*, n.d.) (further information is provided below in section 8.3.3), based on the symptoms of delusions, hallucinations, and depression as an example of a third symptom (the future version of the tool, used in the Component B of the study, included delusions and hallucinations, in addition to a third behavioural symptoms chosen by each caregiver among the symptoms listed in the Neuropsychiatric Inventory – Questionnaire (NPI-Q)). This early prototype was analysed in the first phase of Component A (co-design) of the study (Figure 8.1) and feedback was gathered with three personal interviews (two held in the participants' houses and one at a local café) and two small-scale focus groups (n = 2 participants in the in-person focus group held at the University of Strathclyde and n = 3 participants in the online focus group, which was held on the Zoom platform). Resources such as "The Smarties guide to co-production" (Donaldson et al., 2023) were used to guide the structure and content of the meetings. Content and functionality of the tool (e.g., the relevance and wording of items and symptom descriptions provided at the beginning of each question) as well as of the instruction manual (created to explain how to use the tool on Qualtrics) were discussed, and changes were implemented where possible (the changes suggested and implemented, and opinions of the participants are presented in the results, section 8.4.1). A sub-group of participants constituted by the group of current caregivers (Table 8.1) was then provided with the edited version of the tool to trial for a set period of time ranging from one to four weeks based on participants availability. Lastly, feedback was sought from the four participants via survey, and an interview was held over phone call with three out of the four participants (as one was unavailable and therefore only provided feedback via survey).

In Component B (pilot), the first session was always held in person (normally at the participants' houses with one exception of a dyad who expressed the preference to come to the University, and one who chose to meet at a local Alzheimer's Centre), and it consisted of the collection of neuropsychological, neuropsychiatric and functional data according to the protocol in Table 8.2. Following this, the caregivers were instructed on the use of the tool, based on the co-designed instruction manual, and they were

asked to choose a third symptom to monitor (the first two being delusions and hallucinations). Providing the choice of a third symptom was conceptualised to give the participants the opportunity to monitor a symptom which was relevant to them and of personal interest, in order to provide a short-term benefit to their participation to the study. This type of flexibility embedded in the protocol also allowed to test, and it demonstrated, the potential for personalisation of the tool, which was adapted to each case individually. Following this, the caregivers were left to complete the daily monitoring for a set time period of four weeks (with the exception of a person who completed it for two weeks due to personal circumstances). Lastly, feedback was sought from all participants via survey and an interview held over phone (n = 5) or video (n = 6) call. During this last meeting, caregivers were also asked to answer questions from the Neuropsychiatric Inventory.

Figure 8.1

Procedures of the two study components



8.3.3. Tool development

The tool was initially developed by the researcher with the key feature of allowing for more frequent collection of behavioural data compared to currently available tools, which rely on a clinician's interview, and typically require informants to reflect over the past weeks (normally four) to provide an overall summary of the symptoms experienced by the person with dementia. It was first designed by the research team to capture symptoms of interest to this research programme (psychotic symptoms), including items that correspond to these symptoms in people with dementia. Based on the critical analysis of the ideal features of a digital tool discussed in the introduction (e.g., Pozzi et al., 2023), the questions were developed to be easily and quickly completed by a caregiver of a person with dementia. Similarly, the Qualtrics interface was chosen for its user-friendly features, and easily access through a personalised link, which can be saved on a smartphone or tablet home screen. The content of the tool was initially developed to be completed within ten/fifteen minutes: the questions on three behavioural symptoms (delusions, hallucinations and depression for Component A (co-design) and delusions, hallucinations and a symptom of choice for Component B (pilot)) were preceded by a definition of the behavioural symptom (Figure 8.2), and they were built so that only in the case of a positive answer to the screening question, follow-up questions would be available, otherwise the questionnaire would continue to the following symptoms (following a logic similar to that of the NPI, in order to maximise efficiency for the caregiver's answers (Pozzi et al., 2023)). Each subtype was then further qualified for its severity (range 1-3), frequency (range 1-3), and associated distress (with separate questions relating to both the person with dementia/MCI and caregiver, both ranged 0-3), as illustrated in Figure 8.2, which shows the qualifier for each Likert point. The screening questions for each symptom and the specific sub-questions were based on known symptom phenomenology as investigated in a preliminary review of pre-existing standardised paper-and-pencil scales (among which mainly the NPI (Cummings et al., 1994) and the BEHAVE-AD (Reisberg et al., 1987)), as well as the new proposed criteria for psychosis for the questions relating to delusions and hallucinations (Cummings et al., 2020; Fischer, 2020), and other symptom-specific scales for the other neuropsychiatric symptoms such as the Geriatric Depression Scale (Yesavage & Sheikh, 1986). Participants in the focus groups and interviews were invited to comment on all aspects of the questions posed, from the usefulness and clarity of the symptoms

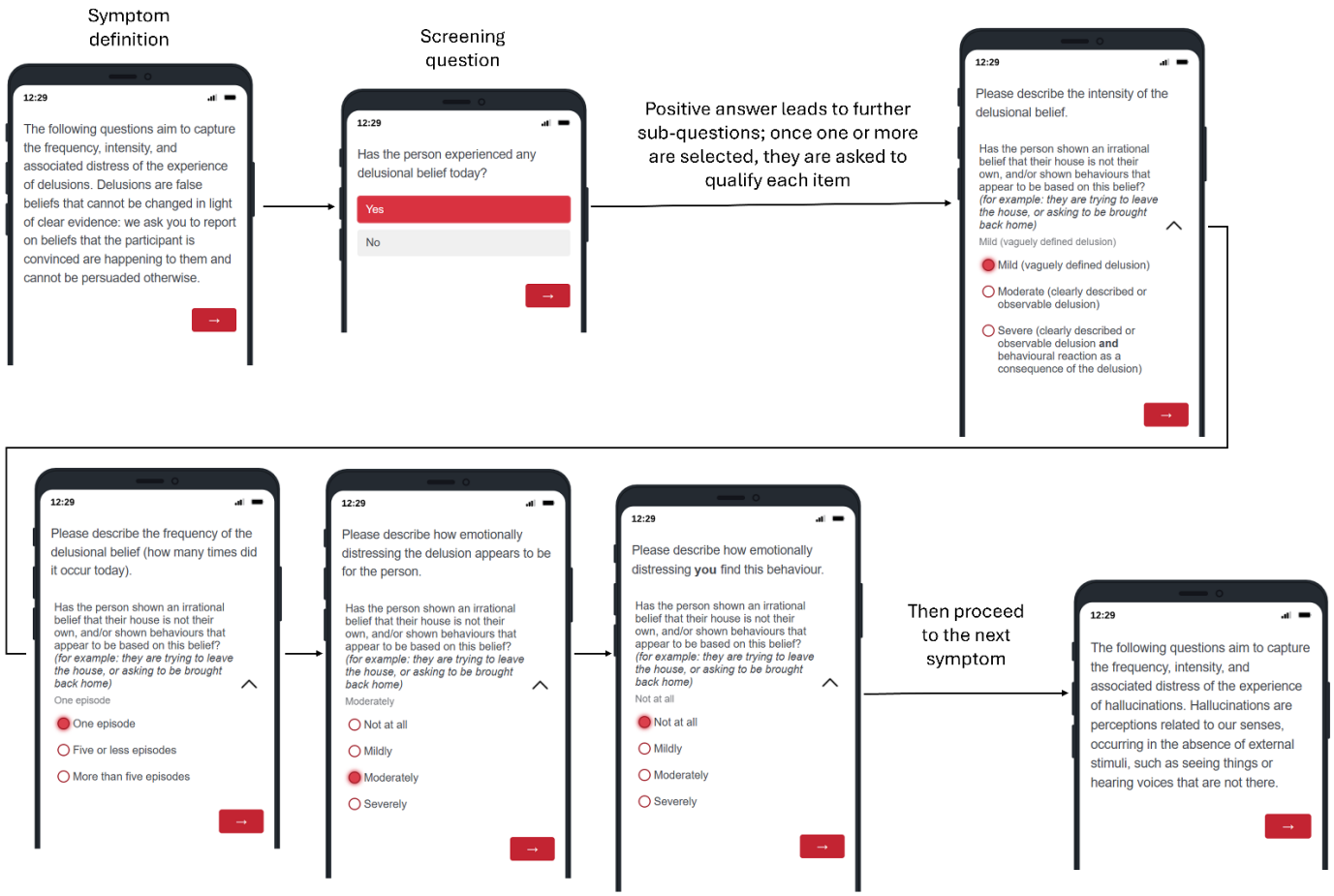
definitions at the beginning of each block, technical elements such as the appropriateness of the wording, clarity of the questions, and ease of use of the Qualtrics layout, particularly to navigate through the subtypes and qualifiers of the Likert scales (their responses are analysed in the results, section 8.4.1). Each block of sub-questions also included the option for the caregiver to report, using free text, any other manifestation of the symptom not indicated by the researcher.

8.3.4. Co-design and feedback analysis

As mentioned in the above sections, prior to the beginning of this study, a first version of the digital monitoring tool was developed, along with an instruction manual detailing how to use the tool on Qualtrics. These were analysed in the focus groups and interviews carried out in phase 1 of Component A (co-design). The focus groups and interviews were run using visual aids in the form of a booklet (available both on paper and digital), where the participants were shown the first version of the tool (using a Qualtrics link) and of the instruction manual, and question prompts were prepared beforehand to aid reflection. Participants were asked to comment on all aspects of the tool and instruction manual, as described in the section above, from technical to conceptual elements such as potential benefits, desirable functionality, suitability of the methodology chosen and relevance of the tool in their experience of disease. Their answers were analysed and used to create the final version of the tool to be applied in Component B (pilot).

Figure 8.2

Visual representation of Qualtrics interface



Following the tool trial in both components A and B, the caregivers were asked to complete a feedback survey, built ad hoc, based on the principles of the technology acceptance model (Davis, 1989; Kjörk et al., 2022), with questions pertaining to usefulness, ease of use, time to complete and potential challenges. Following this, feedback was also sought via semi-structured interviews, where the participants were asked to comment on their experience of using the tool (described in section 8.3.5.4).

8.3.5. Materials

In order to assess the overall neuropsychological, neuropsychiatric and functional profile of participants with dementia/MCI in Component B (pilot), the following assessment tools were administered to participants with dementia/MCI and their caregivers (results are summarised in Tables 8.2 and 8.3). Below is provided a brief description of each instrument, administered in first session (phase 1) to participants with dementia/MCI and their caregivers. Furthermore, in phase 3 of Component B (pilot), the NPI was administered to the caregivers, and in phase 3 of both components, an ad-hoc build feedback interview was administered to the caregivers (both described in following sections).

8.3.5.1. Tests administered to the participants with dementia/MCI in phase 1 of Component B (pilot)

The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was used to assess global cognition and disease severity. The MMSE is comprised of brief tests of spatiotemporal orientation, memory, attention, praxis, and language, scored on a range from 0 to 30 (higher score is indicative of better performance). Typically, people with scores in the 0-13 range are classified as severe, 14-20 as moderate, and 21-26 as mild (Harrison, 2022).

The Repeatable Battery or the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998), developed to identify abnormal cognitive decline in the older adult, yields scaled scores for the five cognitive domains of immediate memory, visuospatial/constructional, language, attention and delayed memory, plus a total scaled score; percentiles based on age and education matched populations are also available.

The Stroop Test (Stroop, 1935) was used to assess the ability to inhibit cognitive interference, occurring when processing a stimulus feature affected by the simultaneous processing of another attribute of the same stimulus (Scarpina & Tagini, 2017). The version used here consisted of three trials of thirty items each, a first one in which words corresponding to the colours of red, blue and green were printed out in black ink and the participant is asked to read them; a second trial with printed coloured (red, blue and green) filled circles, and the participant is asked to say the ink colour; the third trial where words are printed out which read the three colours in random ink of a different colour than the word, and the participant is asked to say the colour of the ink (ignoring the word). It is scored in seconds needed to complete the task and number of errors for each trial. Interference scoring can then be derived by subtracting from the seconds of the third trial (the one which assesses inhibition ability) the average time taken in seconds for the previous two, and the same procedure is repeated for the error scores.

The Wisconsin Card Sorting Test (Berg, 1948) was designed as a measure of executive function, to study abstract behaviour, inhibition and shift of set. The test consists of placing the cards (two decks of 64 each) one by one next to the four stimulus cards (one red triangle, two green stars, three yellow crosses and four blue circles); the participant must deduce the sorting principle from the pattern of the examiner's responses (stating whether the answer is right or wrong) to their placement of the cards (principles are: colour, shape and number). Once the participant has placed the cards correctly for ten times, the examiner changes the principle (again only indicating whether the placement is right or wrong). Typical scoring includes the total switches of categories (which ranges from 0, if the participant does not manage to understand how to switch from one category to the next one, to a maximum of 5 successful switches), and perseverative errors (i.e., errors based on the participant continuous response based on the previous sorting rule, which is indicative of a difficulty in inhibiting the previously correct response and in the flexibility of shifting to a new set).

The Trail Making Test (parts A and B) (Partington & Leiter, 1949; Reitan, 1955) has been developed as a test of divided attention, visuomotor tracking and cognitive flexibility; it consists in connecting circles of numbers (in ascending order) (part A) and connecting circles alternating numbers (in ascending order) and letters (in alphabetical order) (part

B). The two parts were respectively used to assess mainly processing speed and executive function (mostly in relation to cognitive flexibility). They are normally scored in seconds needed to complete each task. Age and education normalised percentiles were also recorded, based on Ashendorf et al. (2008). A ratio measure (TMT-B/TMT-A) can additionally be used, with values greater than 3 suggesting disproportionate impairment in task-switching ability (Clinical Tools Library, 2025).

Luria's three-step test (Weiner et al., 2011) assesses the ability to learn and reproduce a series of three consecutive actions (hand gestures). The most common score is normal/abnormal performance.

As the RBANS only includes digit forward testing, which mainly assesses efficiency of attention and short-term memory (Lezak et al., 2012), a separate digit backward test was also included, to capture working memory. It is typically scored in raw number of digits (longest sequence) remembered; as Lezak suggests, a cutoff of 2 digits remembered indicates impairment, 3 is considered borderline, while 4-5 digits are considered normal.

8.3.5.2. Tests administered to the caregivers in phase 1 of Component B (pilot)

The Neuropsychiatric Inventory – Questionnaire (NPI-Q) (Kaufer et al., 2000) is a brief, questionnaire version of the neuropsychiatric inventory, that the caregiver can complete on their own. It assesses the same twelve neuropsychiatric symptoms to detect their presence within the previous month, only indicating those symptoms that have occurred since the beginning of the memory problems (constituting a change from before the presentation of memory symptoms). It assesses their severity (range 1-3) and the associated caregiver distress (0-5). The NPI-Q was used to aid the choice of the additional symptom to monitor (other than psychotic symptoms which were monitored by all participants), as the caregivers were asked to reflect on the four-weeks period prior to the beginning of participation to the study.

The Functional Activities Questionnaire (FAQ) (Pfeffer et al., 1982) measures instrumental activities of daily living (IADLs), such as preparing balanced meals and managing personal finances. Each item is scored from 0 to 3, with higher scores indicative of partial or total dependence, for a total sum score of 30 (cut point of 9,

therefore dependent in at least 3 activities, is recommended to indicate impaired function and possible cognitive impairment).

A Symptomology Questionnaire, developed by Dr Lydia Grace and Dr William J McGeown (unpublished), which measures behavioural, cognitive and neuropsychiatric symptoms based on the following domains: 1. semantic memory, 2. episodic memory, 3. orientation, 4. delusional beliefs, 5. hallucinations, 6. depression, anxiety, apathy and emotional regulation, 7. behaviour, personality and conduct, 8. executive function and attention, 9. language, 10. additional questions. The caregiver is asked to answer on a scale from the item being never (zero times) present, occasionally (1 to 5 times), frequently (6 to 10 times) or constantly (more than 10 times), on the last month (or a typical month from the recent past). Based on this, scores are provided for each domain ranging from 0 to 24 for the domains 1 to 9 and 0 to 33 for the additional questions.

8.3.5.3. NPI administered to the caregivers in phase 3 of component B (pilot)

All the above assessment measures were administered during the first visit (phase 1) of the Component B (pilot).

In phase 3 of Component B (pilot), which consisted of a final video or phone call, the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) was administered in order to perform a preliminary comparison of the performance of the digital monitoring tool with the current diagnostic standard. As seen in previous chapters of this thesis, the NPI is a retrospective, informant-based rating scale, within which the interviewer poses a screening question for each neuropsychiatric symptom to assess behaviours that have appeared or changed since the onset of illness. The scoring system of the NPI allows coding of the presence of the symptom, as well as the frequency (on a scale of 1-4), severity (1-3), and total score, which is the product of the two measures (1 to 12), and caregiver distress (0-5).

8.3.5.4. Interview administered to the caregivers in phase 3 of Components A (co-design) and B (pilot)

The semi-structured interview for feedback collection was created ad hoc, and it was administered to the caregivers in a complementary fashion to the feedback survey at the end of both components of the study; this format of interview was chosen to allow flexibility to provide space for participants to express their perspectives, and to allow the

researcher to follow up with further questions based on the participants' answers. The main questions posed were: 1) Can you describe your experience using the digital tool? *(prompts if needed: did you encounter any difficulties; how long did it typically take to complete; did you find it useful)*; 2) Can you provide any comments on any potential improvements or additional features that you would find useful to see in future versions of the tool?

8.3.6. Tool performance

The ability of the digital monitoring tool to capture the presence of the symptoms was compared to the NPI (described above), using Cohen's Kappa, sensitivity (true positive rate), specificity (true negative rate), positive predictive value (PPV), negative predictive value (NPV), and accuracy (overall proportion correctly classified).

The metrics of severity (range 1-3), frequency (range 1-3), and distress experienced by the person with dementia/MCI (range 0-3) and their caregiver (range 0-3), captured with the digital monitoring tool are illustrated in Table 8.4, alongside the metrics of severity (range 1-3), frequency (range 1-4) and caregiver distress (range 0-5) as captured with the NPI[2]. The table also reports the additional information captured by the digital tool of total number of occurrences over the time period monitored and any triggers noted. Examples of the description of each value on the Likert scales are illustrated in Figure 8.2.

8.4. Results

8.4.1. Analysis of the focus groups and interviews of Component A (co-design)

As shown in Figure 8.1, Component A (co-design) of the study began with the implementation of two small-scale focus groups and three interviews (phase 1), aimed at analysing the version of the digital monitoring tool initially developed by the researcher to capture the symptoms of interest known from the literature, as well as the instruction manual to support the caregivers in the first use of the tool. It also intended to collect the views of the caregivers on their perceived usefulness and relevance of the

[2] In the NPI, for certain symptoms (i.e., delusions, hallucinations, depression, anxiety and sleep disorders) a measure of distress experienced by the person with dementia is embedded in the severity scoring, while in the digital monitoring tool these two measures are separated.

content based on their lived experiences. The information collected were then reviewed by the researcher, mainly relating to the three elements described below, and the tool and instructions were modified accordingly.

8.4.1.1. Language and explanations

One important aspect on which the participants (caregivers) provided an important contribution was the linguistic registry. No medical jargon was used by the researchers in developing the tool, and for the majority of the questions, the language was deemed appropriate and understandable. However a few edits were made to ensure there would be no ambiguity, and further clarifications to better present the items as observable behaviours were added in brackets where necessary, to ease understanding of sub-questions. It was suggested by one participant who worked in the healthcare sector to provide a clear explanation in relation to the monitoring of symptoms of delusions and hallucinations, i.e. being "careful not to scare people" (Caregiver A4[3]) when discussing psychotic experience while instructing on the use of the tool. Different participants (Caregivers A1, A7 and A8) suggested drawing the caregivers' attention to the potential use of the free writing boxes in the instruction manual, which might otherwise be overlooked, to make the most out of the personal comments. Caregiver A6 suggested to clarify the aspect of regularity in the instruction manual for registering the answers (e.g., every evening, reflecting on the day's events), as providing a structure might help the caregiver organise their schedule around this.

The work on language focused on addressing all potentially ambiguous elements of the tool and of the instruction manual, aimed at overcoming any potential barriers to effective communication (Duffy et al., 2025) in tool instruction and use.

8.4.1.2. Flexibility

An element that was suggested (Caregivers A5, A6 and A8) was to provide a degree of flexibility, for example considering cases in which the questionnaire could not be completed in the evening but the morning after, or to provide the opportunity to come

[3] Participants in this section were coded as Caregivers (A1-8), as this only includes caregivers from Component A; in sections below caregivers belonging to Component B are also included, and coded as Caregivers B1-11, and participants with dementia/MCI as Participants B1-11 in all relevant sections.

back at different times through the day. While this was considered and discussed within the interviews and groups, eventually it was decided against it, to allow for a more regular collection of the data which would lead to clearer outcomes in the form of the summary provided at the end of the month. However, it was agreed that since Qualtrics records the data with a timestamp, participants could, on exceptional occasions, complete the questionnaire the morning after if it had not been possible to complete in the evening, by making it clear that it was referring to the previous day (e.g., reporting this in the free text box provided at the end).

The advantages and potential drawbacks of a flexible approach to data collection were discussed, and it was agreed that a more structured format would allow for a clearer synthesis of the symptoms' occurrences. While allowing less flexibility, it was agreed that such an approach should be favoured for its potential to benefit caregivers who could directly use the outcomes of the research to further their understanding of the symptoms' daily fluctuations and potential communication to healthcare professionals (Granström et al., 2020).

8.4.1.3. Perceived usefulness (pre-trial)

The reception of the tool was positive, with caregivers reporting that "it can be useful to monitor these symptoms, particularly at earlier stages, to be able to understand what's going on" (Caregiver A4), and "look back at what occurred over a period of time" (Caregiver A3). There was general agreement on the idea that the tool would be of particular use at earlier stages of disease (Caregivers A5 and A6), as in their experience, that was the time when, as caregivers, they felt most in need of support, and the opportunity to monitor and have a clear understanding of what symptoms were occurring would have been helpful. Lastly, considering the content, it was overall agreed that providing definitions was useful to clarify the symptoms, and once the few language issues were overcome, the questions were deemed relevant and appropriate.

The perceived usefulness at this preliminary phase of tool development (prior to trialling) was overall positive, and elements were highlighted in line with the idea that caregivers may generally appreciate further support in understanding the symptomology of the person they are assisting (Huang et al., 2025).

8.4.2. Neuropsychological, neuropsychiatric and functional profile of participants with dementia/MCI in Component B (pilot)

In Table 8.2 is reported an overview of all neuropsychological, neuropsychiatric and functional assessment administered to participants with dementia/MCI and their caregivers, reporting the overall characteristics of the sample in terms of minimum and maximum scores, means and standard deviations of all tests (with the exception of Luria's test, for which the number of correct and incorrect performances is reported). An example of the visual depiction of the monitoring is depicted in Figure 8.3, which illustrates participant eight's presentation of psychotic symptoms severity and frequency (Figure 8.3a) and associated distress for caregiver and the participant with dementia (Figure 8.3b). A summary of the measures recorded by all participants is illustrated in Table 8.4, which reports the total (daily) occurrences and if there were any associated triggers, as well as metrics of severity, frequency and associated distress (for the person with dementia and their caregiver) of the symptoms monitored, alongside the NPI scores (severity, frequency and caregiver distress) of those symptoms. In Appendix F are reported each individual's loggings as captured by the tool (i.e., over the period monitored, the scores of severity, frequency and participant and caregiver distress of each sub-type of the symptoms recorded).

Figure 8.3a

Daily monitoring of delusions and hallucinations, Participant B8 (Severity and Frequency)



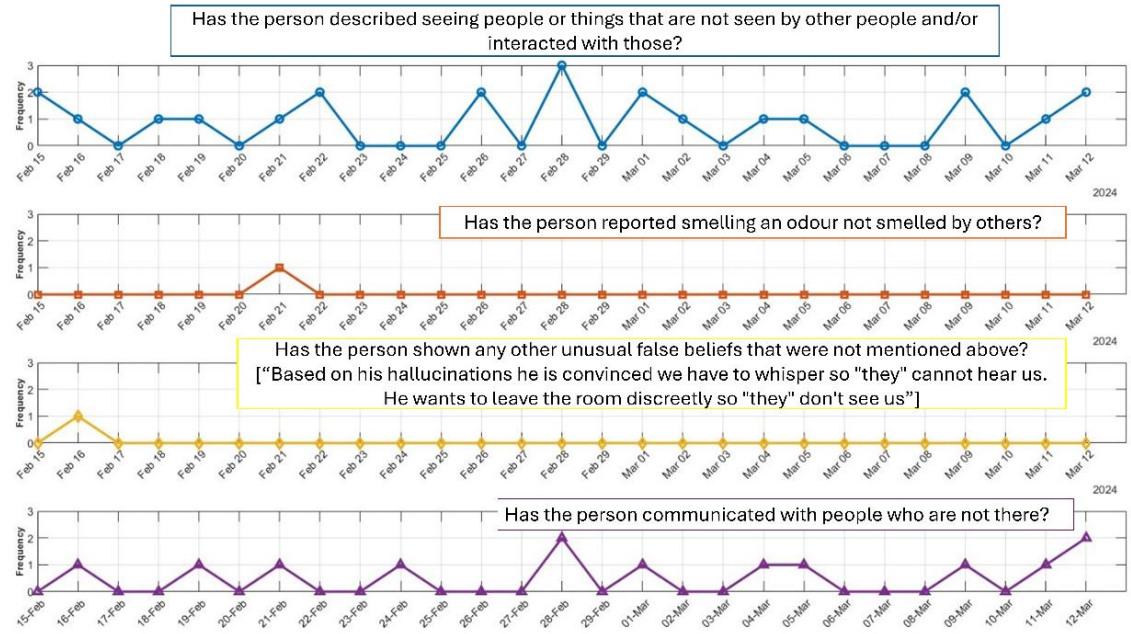


Figure 8.3b

Daily monitoring of delusions and hallucinations, Participant B8 (Caregiver and Person with Dementia/MCI Distress)

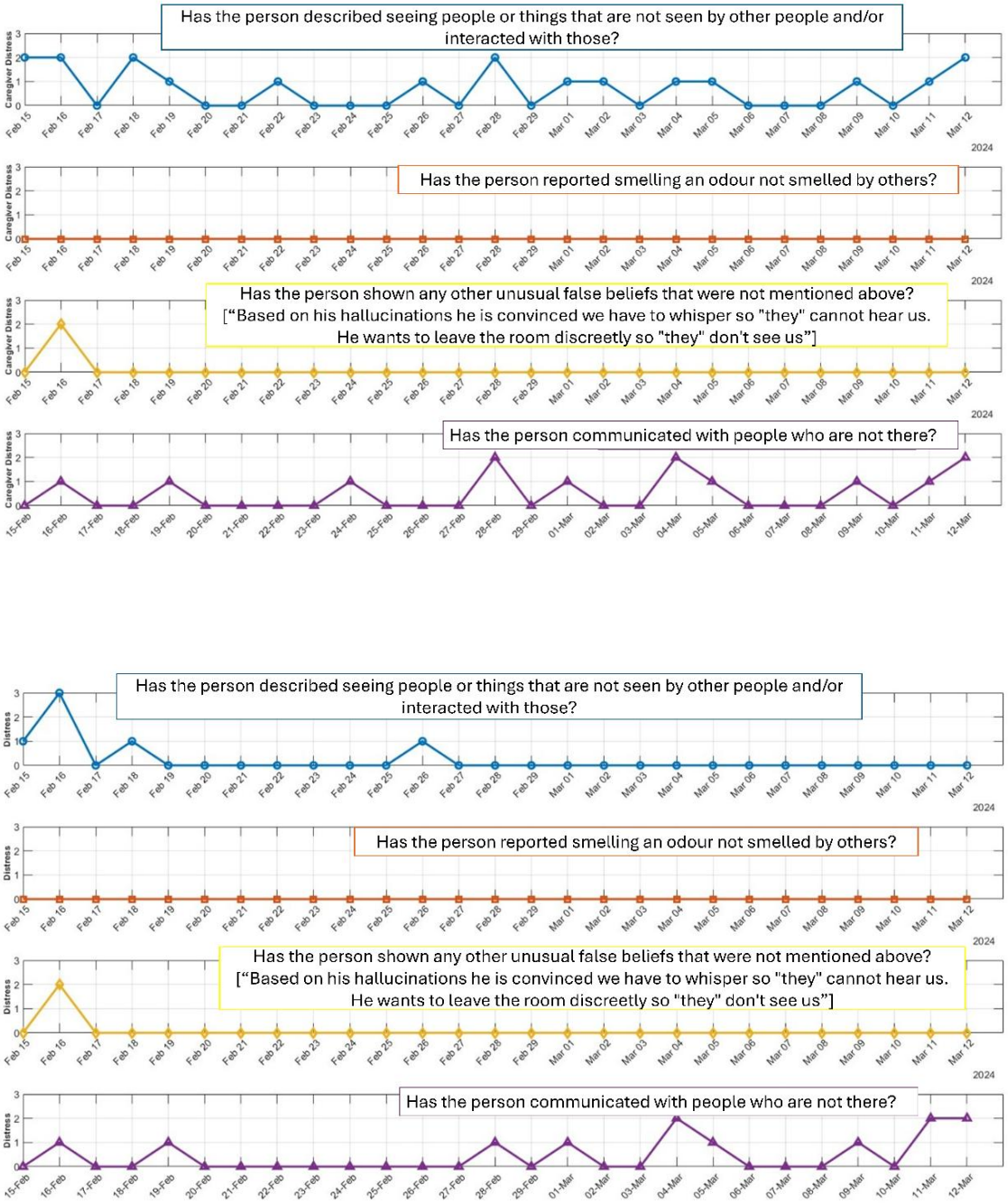


Table 8.2

General overview of neuropsychological, neuropsychiatric and functional assessment implemented in Component B (pilot)

Neuropsychological, Neuropsychiatric and Functional assessment	*M (SD)**	Min/Max*
Caregivers		
Neuropsychiatric Inventory - Questionnaire (NPI-Q)	7.00 (4.26)	Min = 2 Max = 16
Symptomology Questionnaire (SQ, behaviour/cognition/neuropsychiatric)	66.72 (36.83)	Min = 7 Max = 140
Functional Activity Questionnaire (FAQ)	16.45 (9.28)	Min = 1 Max = 26
Neuropsychiatric Inventory (NPI)	11.36 (10.95)	Min = 2 Max = 28
Participants with dementia/MCI		
Mini Mental State Examination (MMSE)	22.36 (7.48)	Min = 3 Max = 30
Repeatable Battery or the Assessment of Neuropsychological Status (RBANS)	67.72 (29.46)	Min = 0 Max = 101
Stroop Test (time interference score)	38.10 (42.29)	Min = 12 Max = 153
Stroop Test (error interference score)	2.50 (3.69)	Min = 0 Max = 12
Wisconsin Card Sorting Test (total switches)	3.00 (1.91)	Min = 0 Max = 5
Wisconsin Card Sorting Test (perseverative errors)	21.00 (13.50)	Min = 6 Max = 44
Trail Making Test part A (TMT-A, in seconds)	73.88 (49.26)	Min = 28 Max = 172
Trail Making Test part B (TMT-B, in seconds)	231.44 (240.50)	Min = 26 Max = 810
Digit Backward Test	3.80 (1.75)	Min = 0 Max = 6
Luria's three-step test (n participants performing correctly and incorrectly)	Correct = 8 Incorrect = 3	

Notes. *For Luria's three-step test these metrics were not reported, as it was scored as correct or incorrect sequence.

Table 8.3

Participants' scores on neuropsychological, neuropsychiatric and functional assessment implemented in Component B (pilot)

Assessment Tools	Participant ID Number										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
NPI-Q	4	3	16	10	4	2	9	9	3	7	10
NPI*	2	3	38	20	8	3	19	13	2	11	6
FAQ	11	1	26	11	24	16	26	23	1	22	20
SQ Semantic memory	8	6	20	7	11	8	12	12	2	2	12
SQ Episodic memory	12	0	15	7	21	11	13	16	8	7	12
SQ Orientation	3	0	20	9	10	5	10	7	0	2	11
SQ Delusions	0	0	2	0	1	1	3	5	0	1	0
SQ Hallucinations	0	0	3	0	0	0	0	3	0	1	1
SQ Affect	5	0	11	8	4	3	3	6	1	4	13
SQ Behaviour	1	1	3	7	8	4	5	3	1	9	4
SQ Executive function	7	0	22	7	17	18	19	20	1	12	15
SQ Language	7	0	12	3	4	12	4	8	1	4	7
SQ Physical	2	0	10	1	6	9	0	0	0	9	0
SQ Additional	1	0	22	3	6	3	7	11	4	6	10
SQ Total	46	7	140	52	88	74	76	91	18	57	85
MMSE	23	30	3	24	22	18	19	27	30	25	25
RBANS Total score	49	101	NA	60	72	65	52	64	101	99	82
R Immediate Memory	40	87	NA	61	65	69	44	73	100	109	78
R Immediate Memory perc	<0.1	16-25	NA	0.1	1	1-2	<0.1	2-5	50	63-75	5-9
R Visuospatial	72	126	NA	84	105	72	81	60	131	109	102
R Visuospatial perc	2-5	95-98	NA	9-16	63	2-5	9-16	0.4	98-99	37-50	50-63
R Language	74	98	NA	64	82	85	47	85	96	94	92

Assessment Tools	Participant ID Number										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
R Language perc	2-5	37-50	NA	0.4	0-16	16	<0.1	16	37-50	25-37	25-37
R Attention	53	100	NA	56	85	64	75	79	115	82	109
R Attention perc	<0.1-0.1	50	NA	0.1	16	0.4-1	5	5-9	84	9-16	63-75
R Delayed memory	40	95	NA	78	52	71	52	60	64	105	52
R Delayed memory perc	<0.1	37	NA	5-9	<0.1-0.1	2-5	<0.1-0.1	0.4	0.4-1	63	<0.1-0.1
STROOP task 1 (sec)	21	12	NA	22	17	40	202	27	18	17	19
STROOP task 1 (err)	0	0	0	0	0	0	0	1	0	0	0
STROOP task 2 (sec)	33	14	NA	26	20	50	50	25	23	16	20
STROOP task 2 (err)	1	0	NA	0	0	2	0	0	0	0	0
STROOP task 3 (sec)	180	25	NA	51	70	80	141	60	32	32	46
STROOP task 3 (err)	5	0	NA	0	1	3	12	4	0	0	2
STROOP Time Interference	153	12	NA	27	51.5	35	15	34	11.5	15.5	26.5
STROOP Error Interference	4.5	0	NA	0	1	2	12	3.5	0	0	2
Wisconsin Switches	1	5	NA	4	5	NA	NA	0	3	3	NA
Wisconsin Perseverative Error	44	14	NA	6	18	NA	NA	8	29	28	NA
TMT-A raw	75	35	NA	41	43	NA	172	102	28	45	124
TMT-A perc	<2	9-24	NA	25-74	9-24	NA	<2	<2	25-74	3-8	<2
TMT-B raw	270	55	NA	180	190	NA	>300	>300	26	50	164
TMT-B perc	<2	25-74	NA	<2	<2	NA	<2	<2	>98	25-74	3-9
TMT-B/TMT-A	3.6	1.5	NA	4.3	4.4	NA	4.7	3.3	0.9	1.1	1.3
Digit Backward	3	6	NA	3	4	0	3	4	6	5	4
LURIA	1	1	NA	0	1	0	1	1	1	1	1
Cognitive Impairment	AD (mild)	AD (mild)	AD (sev)	B-FTD	AD (mod)	LB (mod)	AD (mod)	LB (mod)	AD (mild)	VD (mod)	MCI (mild)

Notes. Total scores are reported in the columns of the NPI-Q, NPI, FAQ, MMSE, RBANS and Wisconsin (total switches) and total score for each domain of the Symptomology Questionnaire (SQ). The columns Immediate Memory, Visuospatial, Language, Attention and Delayed Memory are reported as the total scores and percentiles of the RBANS scales, and similarly TMT-A and TMT-B are reported as raw scores and percentiles of the trail making tests (both the RBANS and the TMTs percentiles are calculated based on age and education); a further score is reported as the ratio of TMT-B/TMT-A (values higher than 3 indicative of impaired task switching ability) The Stroop test is reported in seconds needed to finish each of the three tasks and number of errors as well as the interference score calculated as T3-((T1+T2)/2) and E3-((E1-E2)/2); the digit back is the number of digits successfully remembered (2 digits remembered indicates impairment, 3 is considered borderline, while 4-5 digits are considered normal), while Luria has a score of 0 if the sequence was incorrectly performed, and 1 if it was correct. *Abbreviations*: B-FTD = Behavioural Frontotemporal Dementia; LBD = Lewy Body Dementia; VD = Vascular Dementia; mod = moderate; sev = severe; R = RBANS. * Full NPI is reported in Appendix F.

Table 8.4

Summary of digital monitoring tool and NPI features of Component B (pilot)

ID	Symptom	N days present* /n total days	Triggers noted (y**/n)	Severity				Frequency				Caregiver Distress				Person with dementia/MCI Distress***		
				Digital tool			NPI	Digital tool			NPI	Digital tool			NPI	Digital tool		
				Total	*M(SD)*	Min-Max		Total	*M(SD)*	Min-Max		Total	*M(SD)*	Min-Max		Total	*M(SD)*	Min-Max
1	Delusions	0/29	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
1	Hallucinations	0/29	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
1	Anxiety	8/29	y (6)	14	1.5 (0.5)	1-2	1	12	1.3 (0.5)	1-2	2	8	0.8 (0.3)	0-1	2	9	1 (0.5)	0-2
2	Delusions	0/27	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
2	Hallucinations	0/27	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
2	Euphoria	4/27	n	9	1.5 (0.8)	1-3	1	12	2 (0.8)	1-3	1	1	0.1 (0.4)	0-1	1	2	0.3 (0.5)	0-1
2	Irritability	3/27	n	6	1.5 (0.5)	1-2	1	7	1.7 (0.5)	1-2	2	0	0 (0)	0-0	1	6	1.5 (1)	1-3
3	Delusions	7/30	n	20	2.5 (0.5)	2-3	2	9	1.1 (0.3)	1-2	1	4	0.5 (0.5)	0-1	2	10	1.2 (0.8)	1-2
3	Hallucinations	4/30	n	11	2.7 (0.5)	2-3	2	8	2 (0.8)	1-3	3	9	2.2 (0.9)	1-3	3	3	0.7 (0.9)	0-2
3	Anxiety	20/30	y (3)	86	2.6 (0.6)	2-3	3	67	2 (0.6)	1-3	4	32	1 (0.6)	0-2	4	73	2.2 (0.6)	1-3
4	Delusions	0/31	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
4	Hallucinations	0/31	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
4	Sleep	6/31	n	26	1.8 (0.3)	1-2	2	14	1 (0)	1-1	4	17	1.2 (0.4)	1-2	3	12	0.8 (0.9)	0-2
5	Delusions	0/25	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
5	Hallucinations	0/25	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
5	Motor	13/25	n	13	1 (0)	1-1	0	38	2.9 (0.2)	2-3	0	14	1 (0.2)	1-2	0	1	0.1 (0.2)	0-1
6	Delusions	0/29	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-

ID	Symptom	N days present* /n total days	Triggers noted (y**/n)	Severity				Frequency				Caregiver Distress				Person with dementia/MCI Distress***		
				Digital tool			NPI	Digital tool			NPI	Digital tool			NPI	Digital tool		
				Total	*M(SD)*	Min-Max		Total	*M(SD)*	Min-Max		Total	*M(SD)*	Min-Max		Total	*M(SD)*	Min-Max
6	Hallucinations	0/29	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
6	Anxiety	1/29	n	1	1 (0)	1-1	1	2	2 (0)	2-2	1	1	1 (0)	1-1	1	1	1 (0)	1-1
7	Delusions	2/30	y (1)	5	1.6 (1.1)	1-3	1	3	1 (0)	1-1	1	3	1 (0)	1-1	1	4	1.3 (1.1)	0-2
7	Hallucinations	0/30	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
7	Sleep	9/30	y (5)	19	1.5 (0.5)	1-2	2	19	1.5 (0.5)	1-2	2	14	1.1 (0.3)	1-2	3	7	0.5 (0.6)	0-2
8	Delusions	1/29	y (1)	3	3 (0)	3-3	0	1	1 (0)	1-1	0	2	2 (0)	2-2	0	2	2 (0)	2-2
8	Hallucinations	16/29	y (4)	45	1.6 (0.6)	1-3	2	35	1.4 (0.5)	1-2	4	32	1.2 (0.6)	0-2	3	18	0.6 (0.8)	0-3
8	Anxiety	8/29	y (7)	20	1.8 (0.7)	1-3	1	15	1.3 (0.5)	1-2	2	19	1.7 (0.4)	1-2	2	20	1.8 (0.6)	1-3
9	Delusions	0/31	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
9	Hallucinations	0/31	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
9	Anxiety	0/31	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
10	Delusions	0/15	-	-	-	-	1	-	-	-	1	-	-	-	1	-	-	-
10	Hallucinations	0/15	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
10	Anxiety	3/15	y (2)	3	1 (0)	1-1	1	3	1 (0)	1-1	1	3	1.5 (0.7)	1-2	1	3	1 (1)	0-2
11	Delusions	0/33	-	-	-	-	1	-	-	-	1	-	-	-	0	-	-	-
11	Hallucinations	0/33	-	-	-	-	0	-	-	-	0	-	-	-	0	-	-	-
11	Depression	8/33	y (1)	18	1.3 (0.5)	1-2	2	16	1.2 (0.4)	1-2	2	17	1.3 (0.6)	0-2	4	14	1.1 (0.2)	1-2

Notes. * This is the total of days in which the symptom was present, however more subtypes of the symptom can be recorded in the same day (Figure 8.3 and Appendix F) **If triggers were noted, in bracket how many occurrences linked to triggers. ***In the NPI, for certain symptoms (i.e., delusions, hallucinations, depression, anxiety and sleep disorders) a measure of distress experienced by the person with dementia is embedded in the severity scoring, while in the digital monitoring tool these two measures have been separated. *Abbreviations.* M = mean; SD = standard deviation; min = minimum; max = maximum.

8.4.3. Tool performance

The digital tool performance was evaluated by comparing it with the NPI. First, this was assessed based on the presence/absence of the symptoms, generating very good metrics as shown in Table 8.5 and the confusion matrix in Figure 8.4; the two measures showed a moderate agreement as shown with Cohen's Kappa (κ=0.763, 95% CI: [0.516, 0.941]). In most cases negative and positive answers to the NPI corresponded to what registered with the monitoring tool in the previous months, with few inconsistencies (two entries were answered positively to the NPI and negatively to the digital tool, and two were answered negatively to the NPI that had positively appeared in the digital tool). These cases were discussed with the caregivers after the interview. In the two cases that were positive in the NPI but negative in the tool, the reason was that the NPI was held at a delayed time compared to the other participants, i.e., more than one month after the tool trial completion, due to personal reasons of the participants; therefore, while reflecting on the symptoms occurred during the monitoring timeframe, symptoms that had occurred more recently were incorrectly thought to have been present during the period of the tool trial. In the two cases where negative answer was recorded with the NPI which had appeared in the digital tool, one person who chose to monitor the symptom of aberrant motor behaviour did not think that the NPI screening question was relevant to their particular circumstances and symptom presentation (while the tool was more comprehensive in the manifestations of the symptom captured); another one only recorded one episode of delusions during the tool trial, and forgot about this having occurred when asked about it in the NPI interview.

Lastly, based on the observation of the metrics that relate to the severity, frequency and associated distress of the symptoms as captured by the digital tool (e.g., considering the average scores, the range of scores recorded, the sum of the scores (total), as well as the number of occurrences per month) and the NPI, as shown in Table 8.4 these appear comparable for most participants. There were two instances (as reported by Caregivers B2 and B4) where the frequency of the symptoms appeared greater with the NPI than with the digital tool, and similarly in two instances (as reported by Caregivers B8 and B11) the caregiver distress NPI score appeared higher than what registered with the tool. On the other hand, with the NPI, Caregiver B8 appeared to underestimate the severity of all three symptoms recorded with the tool. The reasons for these discrepancies may

differ: for Caregiver B8, by looking at the monthly fluctuations (Appendix F), it shows that more symptoms were occurring towards the end of the month; furthermore, in the score and in the reflective notes at the end, significant distress was linked to the hallucinatory symptoms in the last few records (which was not distressing to her at the beginning of the month, due to the changing nature of the hallucinations). Caregiver B4, on the other hand, reported that the symptoms were very distressing to her from the beginning, which might have led to an overestimation of the symptoms' frequency over the four weeks. In the case of Caregiver B11, the NPI collection was done with a considerable delay from the monitored month, and it was reported that in the time elapsed, more symptoms had occurred which might have affected the memory of the caregiver's feelings in the month monitored.

Table 8.5

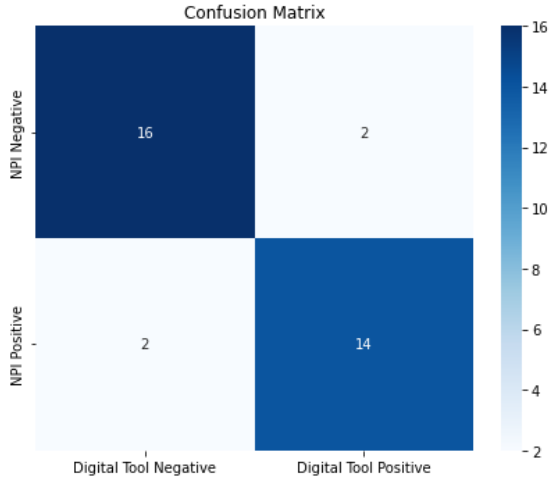
Tool performance metrics

Metric	Value (at 3 decimal points)
Sensitivity	0.875
Specificity	0.888
Precision	0.875
NPV	0.888
Accuracy	0.882
Cohen's κ	0.763

Notes. Data reported in this table is calculated on the basis of all measurements for all participants of Component B (three symptoms per ten participants, and four in the case of Participant B2, for a total of 34 records), similarly to what shown in Table 8.4.

Figure 8.4

Confusion matrix illustrating the raw values of symptoms assessed using the digital monitoring tool and the NPI



Notes. The confusion matrix is calculated on the basis of all measurements for all participants of Component B (three symptoms per ten participants, and four in the case of Participant B2, for a total of 34 records), similarly to what shown in Table 8.4.

8.4.4. Feedback: satisfaction survey and interviews

In both components, feedback was sought from the participants (typically the caregivers, however where possible participants with dementia/MCI were included in the conversation) using a satisfaction survey, followed by a phone interview, in which questions were asked with respect to the experience of using the tool, with the encouragement to comment freely on any aspect they wished to discuss, particularly related to any difficulty encountered, ease of use and perceived degree of usefulness and any improvements they would apply to the tool. The results of the satisfaction survey are reported in Table 8.6, which indicate an overall positive reception: the majority found it quick and easy to use, useful to reflect on the daily events, indicating that it would be helpful to receive such periodic overview of the events and they would be happy to use similar tools in the future; a few answered neutrally on the items relating to the perceived usefulness. Overall, similar comments were collected within the interviews, which

however added some information to further contextualise the responses. The answers from both components are synthesised and discussed below.

8.4.4.1. Usefulness (post-trial)

The main argument that was made with respect to the usefulness of the tool concerned the element of reflection, which was mentioned by about half of the caregivers across both parts. Caregivers mentioned that it was useful for them to "reflect and take notes" (Caregivers A2 and B3). Some highlighted the relevance of the question posed at the end of the questionnaire which prompted them to note down any other comments, such as "Is there anything you would like to add about today's experiences that has not been captured by the questions in the previous sections?", which in some cases might have been related to the behavioural symptoms: one caregiver answered "It was good to reflect on the day, [...] I found it useful to focus on their anxiety and what might have triggered an anxious response" (Caregiver B1), while another said "It was a good chance to reflect on how the day had gone and the impact of the symptom, over time especially [...] it also helped me reflect on external events and compare this to the symptoms" (Caregiver B8). One further caregiver also commented on their perceived usefulness in relation to the element of having the opportunity to share their experience, commenting that this helped making them "feel less isolated" (Caregiver B9) and another mentioned that if felt like "the second-best thing to having a regular contact with a doctor" (Caregiver A1). While most found the questions pertinent to their experience, one (Caregiver B5) mentioned that only two sub-questions of the chosen symptom were applicable, and it would be more useful to have further personalisation.

Overall, it appears that the use of the tool might help caregivers to reflect on the symptomology in a guided and structured way, and this element might have potential to be employed in healthcare settings, to support caregivers to alleviate their burden deriving from a lack of understanding of the symptoms, and feelings of isolation (Kales et al., 2015), by providing a way to make sense of their experiences and receiving timely feedback. Furthermore, the identification of potential triggers would allow the further understanding of key symptoms mechanisms and the development of appropriate intervention and management strategies (Smith et al., 2020).

8.4.4.2. Ease of use

No caregiver reported encountering difficulties while using the tool, and most mentioned that “it didn’t take long to complete” (e.g., Caregivers A1-4 and B2, B6, B8 and B11). The majority commented on the tool looking overall “straightforward” (Caregivers B1 and B8), “intuitive and user-friendly” (Caregiver B2), and the symptoms definitions and questions “understandable” (Caregivers B7 and B11).

In line with the idea of creating a simple tool that overcomes the barriers to participation in digital trials in older adults, the format and completion time received a positive reception, suggesting that a design that considers the needs of caregivers (Pozzi et al., 2023) is likely to generate positive feelings and foster effective collaborations (Cho et al., 2025; Duffy et al., 2025).

8.4.4.3. Suggested Improvements

When prompted to reflect on potential improvements which could be added to the tool, different elements emerged, particularly in relation to further personalisation of the tool. A caregiver focused on technical feature personalisation: “It would be useful to have the option of increasing the font or changing the colour-scheme, adding in some settings preferences” (Caregiver B6). Similarly, two mentioned that it would be useful to “build in a reminder” (Caregivers B6 and B11) that would notify that it is time to record the answers, and another mentioned it would be useful to have the “flexibility” to go back to the tool more times throughout the day to add in things as they happened (Caregiver A4, B2 and B3). Another mentioned that it would be useful to “building in an off-line mode to complete it if the signal goes down” (Caregiver B8), rather than having to rely on a functioning web connection. Importantly, a few mentioned they would appreciate having more opportunities to make the tool more personalised with respect to the questions: “It could be more specific, tailored; it would be useful to give the chance to make the answers more personal and give space to explaining feelings and triggers” (Participant B2).

The element of personalisation, of both format and content, was overall proposed as the most relevant suggestion to improve the experience of symptom monitoring in this manner. Future versions of the tool could be developed that take these aspects into consideration and explore further options to adopt a more tailored approach.

Table 8.6

Feedback survey

Item	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Some-what agree	Strongly agree
I found it easy to use the digital monitoring tool			1	2	4* 8
I experienced negative feelings (for example, stress or anxiety) in relation to the items of the digital monitoring tool	4* 8	1		1	1
Completing the digital monitoring tool helped me reflect on the daily events			3	1* 5	3* 3
I found it time consuming to complete the digital monitoring tool	4* 6	5			
I would be happy to use this or a similar digital monitoring tool in the future			1	4	4* 6
I would find it useful to receive a visual depiction of the data recorded with the digital monitoring tool			2* 2	8	2* 1

Notes. The survey was completed by all caregivers from components A and B. * The first row corresponds to the answers of the caregivers of Component A (Co-design), the second row to the caregivers of Component B (pilot).

8.5. Discussion

This project sought to co-develop and explore the feasibility of a novel digital tool aimed at monitoring the fluctuations, as well as frequency, intensity of the occurrence, and impact on both the participants and their caregivers, of psychotic and other neuropsychiatric symptoms of dementia, through daily collection. This was achieved by performing a study divided into two components: a first component which involved the participation of former and current caregivers of people with dementia, who provided their expertise based on lived experience to co-design the tool and its supporting information manual; a second component (built upon the first one), in which dyads of

participants (caregiver and person with dementia/MCI) pilot tested the co-designed tool. The overarching goal was to collect feedback from the intended users of the tool in both components of the study, on its features, focusing on the perception of the tool in respect to aspects such as usefulness, ease of use and desirable functionality. To the author's knowledge, this is the first project in which a digital tool is applied to the daily monitoring of neuropsychiatric and psychotic symptoms of dementia, centred on the experiences of people with cognitive impairment and their caregivers. The data collected has allowed to reflect on several aspects in relation to its potential applicability, as will be discussed below.

8.5.1. The advantages of more frequent monitoring of neuropsychiatric and behavioural symptoms for a personalised approach to assessment

One of the primary goals of this project was to perform a preliminary investigation to compare the performance of the proposed digital tool, compared to the current gold standard, the NPI: the level of agreement achieved was very good, potentially suggesting high convergent validity, as there were only four cases (two negative and two positive) of discrepancy out of the total (thirty-four) collected records of the symptoms across the eleven participants. Similar results had been previously achieved by Rangseekajee et al. (2021), who tested the performance of a mobile application version of the NPI and had found good internal consistency, as well as a positive reception by the users. Additionally, symptoms that had not been identified before the tool trial, with the NPI-Q (in six instances out of the total sixteen positive collections) were captured with the monitoring tool and subsequently with the NPI (four of these were psychotic symptoms). This might suggest that bringing the caregivers' attention on specific behaviours, with careful symptom definition and selection of subtypes, might lead to a more precise and timely assessment compared to the single interview or questionnaire, in which they might be underestimated. Similarly, it made it possible to consider potential over- and under-estimation biases and importantly, reflect on potential factors that may have caused them, which may help future research on caregivers' attitudes towards neuropsychiatric symptoms.

Importantly, this tool was designed to add four main elements that no other neuropsychiatric assessment currently includes: the daily monitoring, the opportunity for the caregiver to note down reflections on the daily occurrences that might relate to

the symptoms, the impact that these symptoms have on their quality of life, and the outcome synthesis of the recorded answers in the form of an easily interpretable graph. As highlighted in the interviews and focus groups conducted in Component A, one of the main elements that was considered of value by the caregivers was firstly the opportunity to "make sense" of what was happening with the presentation of neuropsychiatric symptoms, in order to then be able to access support and find strategies to cope with them. The enhancement of knowledge, which is at the core of many psychoeducational and training programmes aimed at informal caregivers, such as the above mentioned iSupport, from the WHO (World Health Organization, 2019), was indeed one of the central elements of the tool, with the symptoms definitions added to support clarity in the identification and understanding of the problem. In addition to this, the specific experience of each individual was central in this study (Leplege et al., 2007). Almost all caregivers in the feedback interviews positively commented on this element, highlighting that the daily monitoring allowed them to take a moment to look back at the events happened in that day; some focused on the importance of the reflective action per se, while others took this forward by saying that writing these comments on the digital tool, knowing that these would be then analysed by the researcher, helped them feel less isolated. As shown in previous literature, the findings indicated that the use of digital tool in interaction with a collaboration between caregiver and healthcare or research professional has the potential to provide a bridge in the gap between the needs of people with dementia and their caregivers and what the healthcare system is currently able to provide (Köhler et al., 2024; Petrovic & Gaggioli, 2020). Furthermore, as an additional element, it was reported that some caregivers involved the participant with dementia/MCI in discussion on their experience of their symptoms, and one of them provided feedback on their experience of the tool alongside their caregiver. This has the potential to foster conversations about autonomy and self-reflection (Köhler et al., 2024) that is not typical of current tools in which the person with cognitive impairment is not normally included in the assessment. Additionally, while analysing the patterns of each recorded symptom, it was possible to identify potential triggers to symptom manifestation, and co-occurrences among the different symptoms monitored: expanding this type of analysis to larger samples might support a precision medicine approach to the development of targeted treatment strategies.

Lastly, in line with the current proposition of the possibility to detect neuropsychiatric symptomology at earlier stages of disease, and at times preceding cognitive symptoms (Ismail et al., 2017; Ismail et al., 2016), the presence particularly of symptoms relating to mood, anxiety, and in one case delusions, was noted to be presented by participants with MCI and mild AD, who scored within or above average on most cognitive tests. On the other hand, higher frequency of psychotic symptoms was found in participants presenting with severe stage of AD and Lewy Body dementia, which was expected based on previous literature (e.g., Almeida et al., 2024).

While this was a short-term trial of the tool, it is the author's belief that its use over an extended period of time might significantly support and integrate current assessment methods, and facilitate an effective interaction and greater involvement between people with cognitive impairment and their caregivers and the healthcare system (Granström et al., 2020).

8.5.2. Co-design approach, reception and suggested improvements

This project was designed based on the principles of co-design and PPIE, in adherence with current national guidelines for researchers (*National Institute for Health and Care Research*, 2024) and importantly with the goal of co-creating a resource that would reflect the desired functionality of the intended users. A review by Huang et al. (2025) has highlighted the importance of designing user-friendly technology, supported by clear instructions and minimised technical complexity, in order to enhance engagement by reducing the cognitive load. By integrating the suggestions of people with lived experience throughout the project, the aim was to test the usefulness of this type of technology, considering the importance of not aggravating caregivers' burden (Sohn et al., 2023) by creating a tool which would not be time consuming or request excessive cognitive load. On the contrary, as the review by Sohn et al. (2023) suggested, digital technology when properly developed with the users' needs in mind has the potential to improve communication, ultimately reducing caregivers' burden by facilitating the monitoring of the person with cognitive impairment. By providing a space for daily reflection, which is then analysed and summarised in a graph that can be easily interpreted and used directly by the caregivers, the digital tool can assist the caregivers in understanding and communicating the behavioural changes they witness and, by

showing these, or modified versions, to healthcare providers, be able to access further, specific, appropriate and tailored support in a timely manner.

As the first trial of a digital monitoring tool for behavioural symptoms in dementia, the overall reception was extremely positive: the caregivers found it quick (under 10 minutes) and easy to use, and importantly, they found it useful to reflect on the daily occurrences of the symptoms. Fourteen out of fifteen caregivers across the two components of the study reported they would be happy to use this or a similar tool in the future, and interest was expressed to add new features to it to make the experience more personal. This is in line with what was expected, based on previous work which had involved the participation of caregivers with digital tools of different kind, as seen in recent qualitative studies (Wichmann et al., 2021; Xia et al., 2025) and reviews (Huang et al., 2025; Petrovic & Gaggioli, 2020). Particularly, the two above-mentioned reviews have highlighted that projects involving digital tools aimed for example at psychoeducation or interventions programmes are particularly effective when tailored to the caregivers' needs, which is what this study sought out to do.

Additionally, improvements of the tool suggested by the caregivers of both parts of this study after having trialled using it have also been in line with this later aspect, suggesting further personalisation both in a structural sense (e.g., adding options to changing the font, adding in automatic reminders) and relative to its content, therefore providing more space for the caregivers, and people with cognitive impairment and dementia where possible, to provide greater details on their experience of the symptoms, which are not always captured by standardised questions. A future development of this project might therefore focus on creating a tool that is even more personalised and person-centred, aligning with the idea that precision medicine approaches have the potential of representing the future in AD assessments and interventions (Arafah et al., 2023).

8.5.3. Limitations

Some limitations should be acknowledged. First, it should be noted that participants who sign up to the online recruitment platform "Join Dementia Research", and were therefore contacted for participation in this project, might have a working digital literacy, which might have positively reflected in the overall reception of the digital monitoring tool. In terms of geographical representation, participants were recruited within

Scotland Central Belt, to allow for in-person meetings to occur. While it was important to involve participants who would find it difficult to travel, overcoming this barrier to inclusion (all meetings' locations were chosen by the participants, and these were more frequently their homes), due to traveling availability of the researcher, the area had to be restricted to the vicinity of Edinburgh and Glasgow. With respect to the collection of neuropsychological and neuropsychiatric data, the protocol was flexibly adapted to the needs of participants, thus resulting in some missing data as shown in the results section. Above it was mentioned that it is the author's belief that bringing the caregivers attention on the symptoms monitored for a month might have contributed in some cases to a positive answer on the NPI, which had been missed with the NPI-Q. While this might represent a potential advantage of using the tool, suggesting an increased awareness of certain symptoms after the monitoring trial, it might also suggest that the association between the NPI and the digital tool might have been inflated, as the NPI answers might have been more accurate than normal, given the daily reporting over the period that participants reflected on. While in some cases it was noted a slight over-estimation of the frequency and associated distress of certain symptoms, which could be linked to different aspects such as memory-related recency effect, in the majority of the cases the NPI answers accurately reflected the daily recordings. Lastly, this study did not include a specific and formal protocol for the recording of potential serious or concerning material reported by the caregivers during the tool trial; future, larger scale studies would benefit from including this. While this was only a pilot study, future directions of this research could include further development of the tool, and the potential for testing this within a larger trial, to more fully examine utility, symptom fluctuations, interactions, associations with other symptoms, reliability and validity.

8.6. Conclusions

In conclusion, the aim of this project was to assess the feasibility and pilot a novel digital tool to monitor neuropsychiatric and behavioural symptoms of dementia, with the intention to optimally capture the key features of these symptoms through daily collection. The project was developed using a mixed-method design, where the views of current and former caregivers, as well as participants with dementia, were analysed to inform on the tool's desired functionality, and the tool performance was compared to current diagnostic standard (NPI). The results are promising, as the overall reception of

the tool was really good, and its performance comparable to that of the NPI. Importantly, the tool was considered useful in allowing daily reflection on the behavioural occurrences, with the summary graph of the monitoring later made available to track and report, thus potentially bridging a gap between the caregivers' needs for consistent and timely support and the availability of the healthcare system. A key design feature of the tool that was considered at its inception was to facilitate the assessment process of behavioural symptoms, aiding the work of healthcare professionals by allowing the caregivers to accurately track the presence and associated features of these symptoms. Future versions of the tool would benefit from further personalisation of the structure and content, in order to build a more detailed behavioural profile for each user, which can then be used to access the appropriate care.

Chapter 9: General Discussion

9.1. Overview

This final chapter provides a general discussion, integrating all the studies and systematic reviews of this thesis. Within the first section, a summary of all key findings is provided, following the order of the chapters, with references to the aims, objectives and research questions of the thesis that were introduced in the first chapter, and how these have guided the structuring of all chapters. Links between the studies are also highlighted (for example synthesising how the findings of the systematic reviews guided the development of the independent studies). Next, the implications for future studies in the field of psychotic symptoms in Alzheimer's disease are provided, synthesising the dual aims of this thesis: first, outlining the lessons learned from the novel approaches to analysis of the underlying mechanisms of psychotic symptoms; then, discussing the implications for a novel approach to assessment. Lastly, the key strengths and limitations of this thesis are discussed.

9.2. Summary of key findings

In the first chapter of this thesis, an introduction to Alzheimer's disease (AD) was provided, outlining the neuroanatomical and cognitive profiles, and then providing a detailed overview of neuropsychiatric, and within these psychotic, symptoms, which are the key object of investigation of this thesis. While defining psychotic symptoms, an argument has been formed around the importance of considering different thematic components to investigate key associations of these manifestations, and a holistic view of psychotic symptoms was introduced which showed the value of complex models which consider the interaction of different types of underlying features. The chapter concluded outlining the rationale for the studies of this thesis, based on the identification of four main gaps in the literature: 1) the lack of a clear analysis on how psychotic symptoms cluster over time at different stages of the AD continuum; 2) the lack of recent systematic reviews that synthesise the findings of all available association studies between neuroanatomical and neuropsychological features and psychotic symptoms; 3) the potential to apply novel approaches to statistics and data science to the study of psychotic symptoms, and focusing on different psychotic manifestations; 4) the potential value of a novel tool which allows for a frequent monitoring of psychotic

(and other neuropsychiatric) symptoms for a more personalised approach to assessment.

Based on this, the aims of this thesis were identified as outlined below.

Aim 1: to investigate the nature of different manifestations of psychotic phenomena, by clarifying their trajectory and association with other neuropsychiatric symptoms over time, by systematically investigating previous research on their neuroanatomical and cognitive correlates and by proposing and carrying out novel analyses that address the gaps identified by the reviews.

Aim 2: to develop and test the feasibility of a novel tool which is meant to provide more accurate information, based on more frequent and person-centred data collection.

While aim 1 guided the development of the two systematic reviews and the first four independent studies (chapters 2 to 7), aim 2 guided the development of the last study (chapter 8). Below, a brief overview of the key findings of each study is provided, referencing their objectives, research questions and hypotheses. Figure 9.1 outlines how the findings of each chapter influenced and/or informed the others.

Study 1 (chapter 2) was designed to investigate how neuropsychiatric symptoms, including delusions and hallucinations, may cluster over time, and how the clustering might be impacted by disease progression, considering both Mild Cognitive Impairment (MCI) and AD dementia. What this study found was that although some degree of consistency existed for certain symptom clusters, a single factor structure was not identified across the time points and that fitted both people with AD dementia and MCI. Within AD, it was possible to identify clearer syndromes at earlier stages, while at the latest time points, the symptoms tended to overlap in more complex clinical pictures. For example, there were clusters comprised of agitation and irritability (hyperactivity symptoms), anxiety and depression (affective symptoms), and delusions and hallucinations (psychotic symptoms). Focusing on psychotic symptoms, while these were frequently found to cluster together in AD, albeit with fluctuations at the different time-points, they never co-occurred in MCI. Importantly, in both AD dementia and MCI they were also found to frequently cluster together with different symptoms, such as anxiety, depression, agitation, irritability, and sleep disorders, with different patterns. At later stages of AD dementia, they formed part of the larger clusters mentioned above,

which might indicate that where presumably neuropathological distribution is greater, the neuropsychiatric associations of psychosis tend to be more complex, and the presence of other NPS should be considered when investigating the overall profile of people presenting with psychotic symptoms. It also implies that while there is a tendency of co-occurrence in the AD dementia stage, there is still a substantial degree of variability in the presentation of delusions and hallucinations in the disease continuum overall.

The objective of the first systematic review and (partial) coordinate-based meta-analysis presented in chapter 3 was to systematically analyse and synthesise the findings of the neuroimaging studies that have investigated the brain regions and networks linked with psychosis in AD, in an effort to clarify the neuroanatomical underpinnings of these symptoms, using a detailed protocol for article discovery and data extraction. In line with the notion of exploring the associations of different psychotic phenomena, the results were discussed both considering psychosis as a cluster of manifestations, as well as with respect to individual symptom types (delusions and hallucinations) and the thematic subtypes (misidentification and paranoia). While some brain regions/networks could be identified that relate to all psychotic manifestations, such as fronto-temporal and occipital areas, and the anterior cingulate cortex, clearer distinctions appeared evident when considering symptom type or thematic differences, with most regions localised in fronto-temporal areas in the case of delusions, and fronto-occipital areas in relation to hallucinations. Further distinctions could also be made between misidentification phenomena, that were mainly related to fronto-occipital areas, and paranoid delusions, mostly associated with temporal areas (there was also a difference in terms of degree of atrophy, with misidentification identified as the most greatly impaired subtype). With respect to the phenomenology, it was noticed that fewer studies focused on the symptom of hallucinations, likely due to the lower prevalence of this symptom type in AD when compared to delusions. Other key findings of this review included the suggested importance of including covariates within the analyses, such as disease severity, level of cognitive impairment, as well as the presence of other psychotic symptoms when investigating individual associations; considering the complementarity of different neuroimaging approaches; providing a detailed measurement of psychotic phenomenology and other neuropsychiatric symptoms to

ensure that unique and shared associations with brain regions and networks can be identified.

Based on the key findings of the systematic review, Study 2 (chapter 4) was then designed to investigate how regional atrophy (investigated using both a Region of Interest (ROI) and whole-brain approach with Voxel-based and Surface-based morphometry (VBM and SBM)) relates to the presence of different manifestations of psychotic symptomology in AD dementia and MCI. This was done controlling for important covariates as described above in chapter 3, and considering psychotic symptoms as a cluster, as well as the individual symptoms of delusions and hallucinations, and the thematic subtypes of misidentification and paranoia. The hypothesis was that the regional atrophy might differ across manifestations, and that the findings of ROI and whole brain approaches might differ to a degree. The findings of this study indicated that certain brain areas such as the fronto-temporal areas link to most psychotic phenomena, mostly in line with the literature from chapter 3, while others appear to be related to specific themes, such as fronto-temporal and occipital areas in relation to delusions, an involvement of the cerebellum in relation to hallucinations and misidentification, and a frontal predominance in association with paranoid and theft delusions. As expected, the overlap across the methodologies was only partial.

Mirroring chapter 3, chapter 5 presented a second systematic review which provided a comprehensive synthesis of all the cognitive functions that have been found to be associated with psychotic symptoms in AD dementia and MCI. The main element of novelty introduced in this review was an analysis of the proportion of studies reporting significant findings relative to the total number of studies that investigated each of the cognitive functions, with the process repeated for each sub-group of psychotic classification. This allowed clearer conclusions to be drawn on the value of functions such as executive function and semantic memory, which were linked to most manifestations, and which seemed to surpass the importance of functions more frequently investigated but which had less associations overall (e.g., episodic memory and language). It was also possible to identify the specific associations of some functions with distinct psychotic classifications (e.g., episodic memory mostly linked to delusions; visuospatial function, frequently associated with misidentification but not greatly relevant to other psychotic symptom classifications). Other implications of this

review (in addition to those already identified from the neuroanatomical review, such as the careful consideration of psychotic phenomena and of important covariates, and more severe symptoms associated with misidentification compared to paranoid delusions) included a potential gap in the use of novel approaches to feature selection when testing the associations of multiple tests within large batteries, and the suggestion to include potentially key underestimated functions in future studies on the cognitive profile of psychotic symptoms.

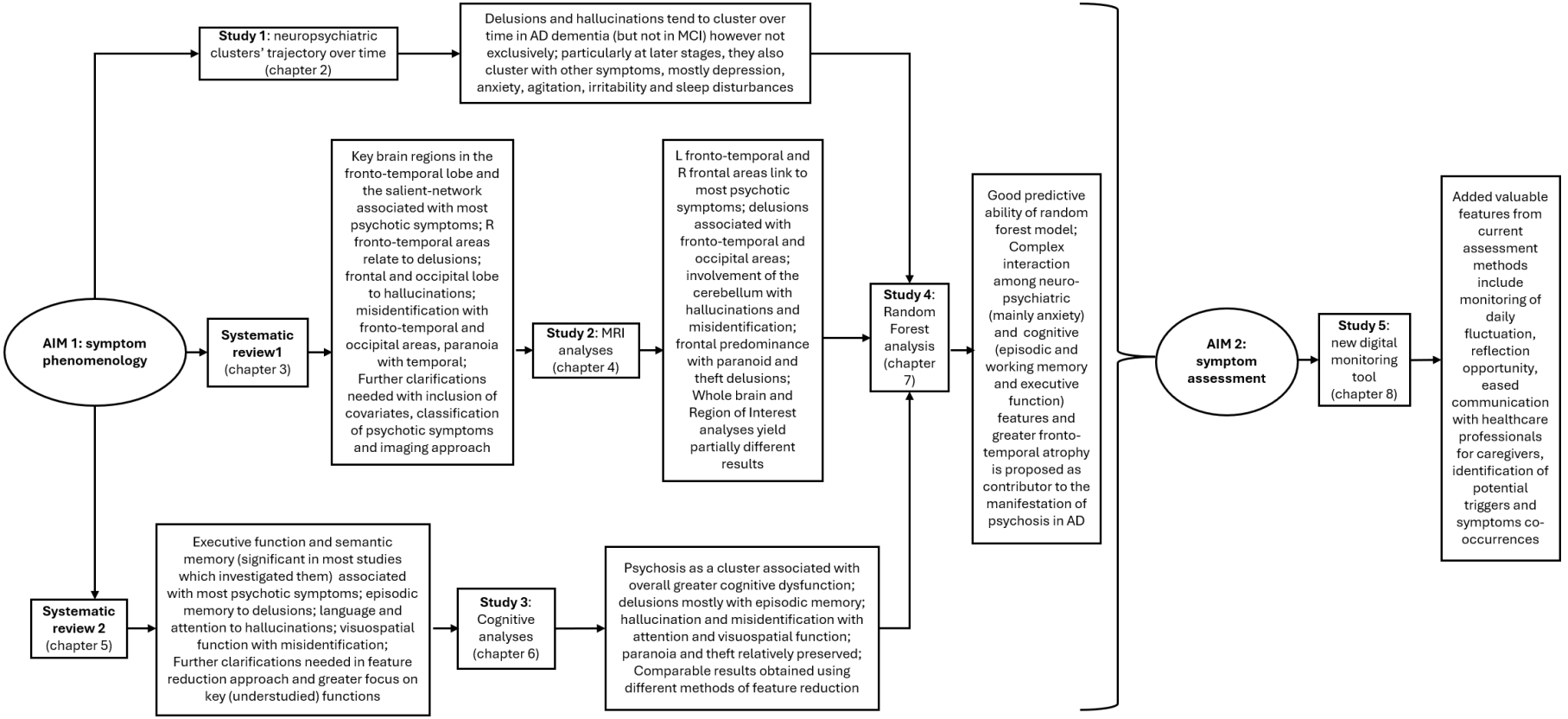
Addressing these key points, Study 3 (chapter 6) sought out to identify the neuropsychological profiles of people who present with different groupings of psychotic symptoms. This was done by performing the feature selection using a data-driven approach (LASSO regression) and a literature-based approach (which considered cognitive domains, using confirmatory factor analysis-based composite scores) considering relevant covariates. The findings indicated that psychosis tends for the most part to be associated with greater cognitive dysfunction, and in confirmation of the hypothesis, greater clarity over specific correlations between psychotic symptoms and cognitive profile were achieved when considering distinct manifestations. This study suggests that delusions tend to be associated with impaired episodic memory (with contributions from other functions such as executive and visuospatial functions), hallucinations and misidentification mostly with visuospatial and attentional components, while participants presenting with paranoia had a relatively preserved cognitive profile compared to controls, with a slight involvement of episodic memory.

In a complementary fashion to the study of the neuropsychiatric, neuroanatomical and neuropsychological co-occurrences from a single viewpoint, Study 4 presented in chapter 7 introduced a novel approach to explore the combinatorial value of the above features in predicting psychosis in AD dementia and MCI, using a machine-learning method (Random Forest Analysis). This study evaluated the predictive ability of a model which identifies the multimodal features which show greater discriminatory potential. The complex interaction among predictors was proposed to contribute to the manifestation of psychotic symptoms in AD, with affective and hyperactivity neuropsychiatric symptoms (most importantly anxiety), episodic and working memory and executive function, and greater fronto-temporal atrophy presenting with higher relevance in the model.

Lastly, addressing aim 2 of this programme of research, in Study 5 of this thesis (chapter 8) a novel digital monitoring tool of behavioural symptoms of dementia was presented, that was designed to optimally capture the key features (symptom fluctuations, as well as frequency, intensity of the occurrence, and impact on both the participants with dementia/MCI and their caregivers) of psychotic and other neuropsychiatric symptoms, through daily collection. This was based on the premise that performing more frequent collection of data might capture the behavioural symptomology more precisely, enhancing understanding of symptom occurrence and triggers, and potentially aiding communication between caregivers (promoting their empowerment through the additional understanding of the symptoms to monitor) and healthcare workers. The research questions this study sought to address were those of exploring the caregivers' opinions on the desired functionality and usability of this proposed digital monitoring tool, exploring the neuropsychological profile of participants presenting with neuropsychiatric symptoms through a person-centred approach, and assessing the performance and potential benefit of the tool compared with the current diagnostic standard, the Neuropsychiatric Inventory (NPI). The overall reception of the tool was very positive, and its performance comparable to that of the NPI, with some added features the caregivers perceived as beneficial, such as allowing timely reflection on daily events, and creating links with potential triggers of the symptoms. This latter element, as well as a precise analysis of symptom co-occurrences, could also further contribute to the research on the underlying mechanisms of neuropsychiatric and psychotic symptoms, as well as having the potential of supporting a tailored design of treatment strategies. Feedback from the participants suggested that in the future, the tool may be further personalised in structure and content, in order to build a more detailed behavioural profile for each user, which could prove useful to access the appropriate care.

Figure 9.1

Summary of studies and key findings



9.3. Implications for future studies in the field

Several important implications derive from this thesis, which may contribute to the understanding of the phenomenology of psychotic symptoms, their associations profile from different perspectives, as well as informing future research in this area. In chapter 1, it was discussed the importance of identifying, among people presenting with AD dementia and MCI, those who might be most at risk of developing psychotic symptoms, to promote the implementation of targeted treatment strategies (D'Antonio et al., 2022; Rose et al., 2025). Through the thorough investigation on the key mechanisms underlying psychotic symptoms carried out in this thesis, it appears possible to propose key features associated with these symptoms, providing rationale for investigating these as a cluster and as individual symptoms. This is discussed in the section below (9.3.1), as well as implications concerning the methodological approaches, which are considered to have potential to improve the quality of future research in this area. In the following section (9.3.2), implications of the new proposed approach to the assessment of psychotic symptoms are outlined, and its potential benefits for participants with cognitive impairments and caregivers.

9.3.1. Implications for the studies on phenomenology of psychotic symptoms and identification of markers for at risk individuals

One of the main implications of the findings outlined within this thesis concerns the possibility to identify profiles of individuals, among those with AD dementia and MCI, who have or might present with higher risk of developing psychotic symptoms, based on a number of key, complexly inter-related neuropsychiatric, neuroanatomical and cognitive predictors (Figure 9.2). This can be approached by considering the mechanisms that may underly all psychotic manifestations, based on the premise that as seen in study 1 (chapter 2) delusions and hallucinations do tend to co-occur in AD. Through this study it was also possible to identify several comorbidities with other neuropsychiatric symptoms, which were also flagged as predictors in the random forest model of study 4 (chapter 7). These include anxiety, depression, sleep disorders, as well as agitation, irritability and apathy, in confirmation of the literature which suggests a degree of co-occurrence among neuropsychiatric symptoms, particularly as the pathology progresses (Gottesman & Stern, 2019). In study 5 (chapter 8), similar types of co-occurrences were identified in some of the participants, where the daily monitoring

of symptoms allowed to follow the specific patterns of manifestation, at times linked to specific triggers such as anticipation of events out of the routine. This seems to suggest that it might be possible, with accurate and frequent reporting of symptoms, as well as of potential triggers or environmental risk factors, to identify targeted management strategies for psychotic symptoms (Isaacson et al., 2018): for example, if a clear link between anxiety and psychosis was established in a person with dementia, in relation to the inability to cope with certain anticipated events, strategies could be explored such as addressing the anxiety through appropriate therapies (e.g., CBT (Regan & Varanelli, 2013)).

Furthermore, through the Random Forest study (Study 4), as well as the two association studies on the neuroanatomical and cognitive correlates (studies 2 and 3), it was possible to identify a key number of neuroanatomical and cognitive features among which most notably greater fronto-temporal atrophy (Chen et al., 2021; Rosenberg et al., 2015), and an overall decline in many cognitive functions, including executive function, visuospatial function, spatiotemporal orientation, language, episodic and semantic memory, which is mostly consistent with the literature (Chatzikostopoulos et al., 2025; Fuller et al., 2019). Such an integrated perspective may represent the beginning of a path towards the application of a routine precision medicine approach, inclusive of psychiatric and psychosocial aspects alongside neuroanatomy and cognition, which is thought to represent the future of AD research (Arafah et al., 2023).

At the same time, as study 1 showed, the clustering of psychotic symptoms is not always stable, implying that there is a degree of variability in the co-occurrence of these symptoms over time, as was expected based on the literature (e.g., Fischer, 2020). Furthermore, the following studies on the neuroanatomical and cognitive correlates (studies 2 and 3) showed that while it is true that some key brain regions and the impairment on a considerable number of cognitive functions tend to correlate with the psychotic cluster groups of participants, clearer profiles emerge when considering the individual symptoms and themes. Overall, as shown in Figure 9.2, certain characteristics appear more clearly when considered in relation to specific manifestations of psychotic symptoms. For example, delusions, and particularly paranoid delusions, appear linked to episodic memory, more than any other cognitive function. Furthermore, when all subtypes of delusions were considered together

(inclusive of paranoia and misidentification), these were mostly linked to temporal lobe atrophy, while frontal atrophy was specifically linked to delusions of paranoia. Misidentification phenomena (inclusive of delusions of misidentification and hallucinations based on the approach illustrated in chapter 1 (Cook et al., 2003; Perez-Madriñan et al., 2004)), were the sub-groups more strongly linked to cognitive dysfunction, and similarly to the sub-groups of hallucinations considered separately, linked to atrophy in the cerebellum, and impairment on functions such as attention, visuospatial function and executive function. In addition, the misidentification sub-group also had greater episodic memory impairment and atrophy in frontal lobe.

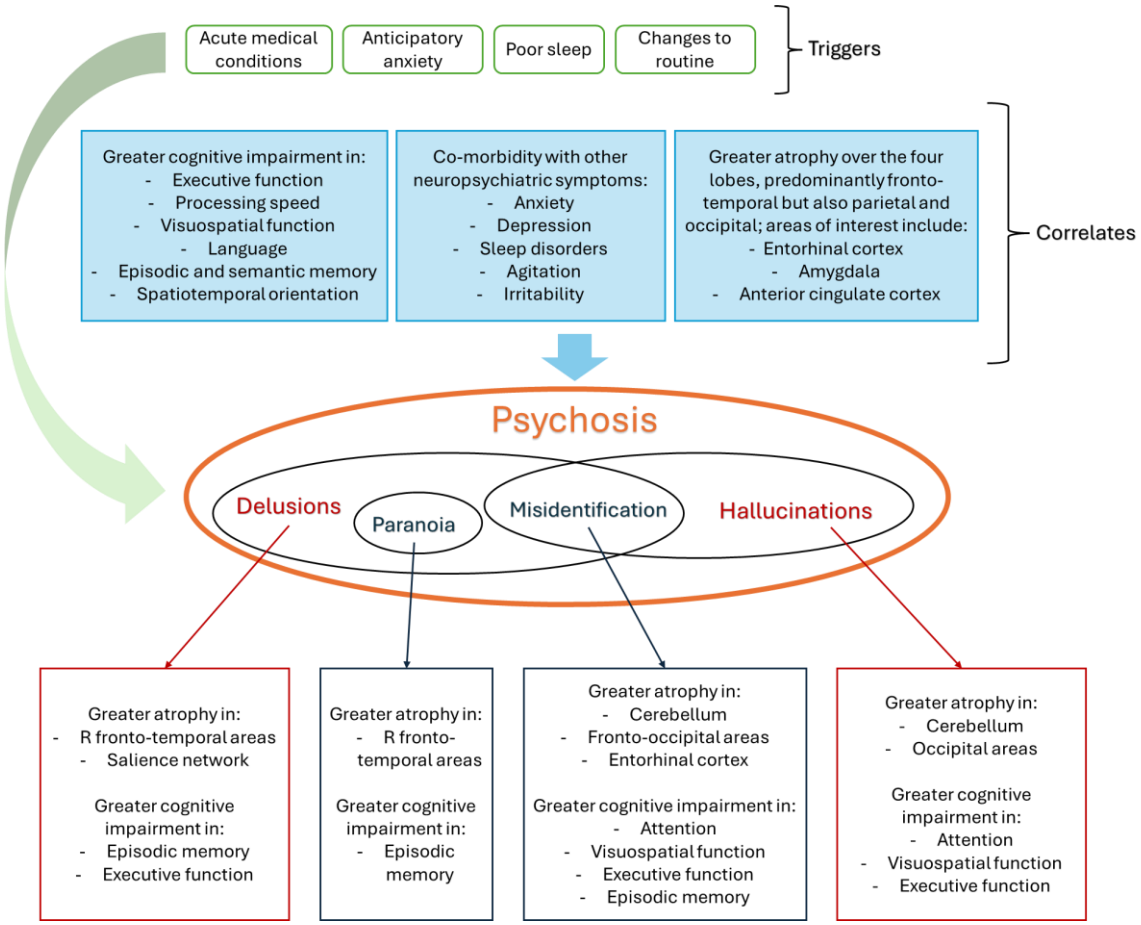
Importantly, the approach to methodology employed in studies 2 and 3 was aimed at reducing potential confounding factors, and this was done by refining the sub-groups in a way that the presence of the other psychotic symptoms were controlled for; this has not typically been done across the literature as seen in the two systematic reviews, and it was believed to be important to achieve unique profiles of associated symptoms. Furthermore, for what concerns study 2, the whole-brain analyses (VBM and SBM) and ROI approaches were compared, to propose an integrated perspective and address potential limitations of one single methodology (Giuliani et al., 2005). In study 3, the potential issue of multiple comparisons and the likelihood of type I errors (false positives), deriving from analyses performed on large test batteries was addressed by comparing the findings of two feature reduction strategies (one based on LASSO regression, and one based on the use of cognitive functions derived from CFA items): this strategy allowed identification of the key cognitive functions which were more evidently and consistently associated with each sub-group. Therefore, through studies 2 and 3, it has been possible to suggest potential markers of each individual manifestation of psychotic symptoms, thus contributing to providing clarity over the mechanisms that underly these symptoms in a novel manner.

As studies 4 and 5 have preliminarily suggested, it appears that it might be possible to create complex models to predict psychotic symptoms of AD considering a high number of variables, and it could be beneficial to monitor the presentation of these symptoms more frequently and considering additional elements compared to what is currently typically done in clinical and research contexts. It stands to reason that the integration of these two approaches would benefit future research, as it would allow the capture of

precise data on the presentation of each psychotic (and neuropsychiatric) symptom (Cho et al., 2023). This could then be used to create complex models, to identify more precise markers of each individual manifestation of psychotic symptoms, as it has been shown that these might substantially differ from one another.

Figure 9.2

Key mechanisms of all manifestations of psychotic symptoms in AD in a multifactorial model



Notes. Starting from the top, potential triggers (identified from study 5, chapter 8), cognitive and neuroanatomical correlates deriving from studies 2, 3 and 4 (chapters 4, 6 and 7), and the two systematic reviews (chapters 3 and 5), and neuropsychiatric from studies 1, 4 and 5 (chapters 2, 7 and 8), in associations with both delusions and hallucinations considered within a psychotic cluster. Below, neuroanatomical and neuropsychological profiles of individual psychotic manifestations, from studies 2 and 3 (chapters 4 and 6), and the two systematic reviews (chapters 3 and 5).

9.3.2. Implication for the assessment of psychotic symptoms: personalised approach to profile and assessment

With regard to the assessment of psychotic and in general neuropsychiatric symptoms, in recent years, several international groups (Cummings et al., 2020; D'Antonio et al., 2022; Fischer, 2020; Pozzi et al., 2023) have proposed different approaches to improve their characterisation and to enhance the diagnostic process in clinical and research settings. The studies of this thesis add to this body of literature, both by providing further understanding of the profile of psychotic symptoms as seen in the previous section, and by proposing a novel, personalised approach to the monitoring of NPS, in line with the recommendations of the above-mentioned research groups. As seen in the previous section, one implication of this thesis is that while assessing psychotic symptoms, it is important to consider the specific phenomenology of these symptoms, as the cognitive outcomes appear to differ based on this aspect, in line with expectations based on the literature (e.g., Lee et al., 2016; Quaranta et al., 2015). Furthermore, the opportunity for a frequent and consistent assessment of NPS has been recently proposed as potentially crucial to achieve a precise assessment of this array of symptoms that is not limited to caregivers' recollections of a specific time period as is typically done with the NPI (Cho et al., 2023; D'Antonio et al., 2022; Morganti et al., 2018; Pozzi et al., 2023). Study 5 proposed in chapter 8 has provided preliminary evidence that more frequent assessment is feasible and well received by caregivers, who, in line with the findings of previous studies (Köhler et al., 2024) have generally welcomed the opportunity to have a space dedicated to their reflection of their experience with symptoms that are notably difficult to manage (Cheng, 2017; Raphael, 2025).

As seen in chapter 8, an element that was considered particularly helpful was the possibility of having a meaningful exchange with the researcher, opening up a conversation which fostered a shared understanding of the symptoms (Duffy et al., 2025; Petrovic & Gaggioli, 2020). It is believed that this could represent a first step to limit the impact of the caregivers' biases in the recollection of the symptoms which could hinder an accurate picture of the person with dementia's clinical profile, in a way that does not directly involve close and constant clinician's observation, which is often not feasible (Granström et al., 2020), particularly in community-dwelling people. Such a tool would have the potential to support and complement the healthcare workload, the

caregivers needs, easing their burden and promoting their empowerment through support and education, and achieving the shared goal of reaching an accurate detection of behavioural changes (Raphael, 2025) oriented at the development of targeted treatment strategies (Pozzi et al., 2023). Working in collaboration with the caregivers and, where appropriate and possible, people with dementia (Kjörk et al., 2022), is in line with most recommendations on the management strategies for neuropsychiatric symptoms (Preuss et al., 2016; Watt et al., 2024) which propose the use of non-pharmacological interventions if possible in a first instance, in a targeted manner based on the identification of individuals' needs and modifiable risk factors. One important use of the tool could therefore be that of focusing on identifying triggers and developing interventions that target those. As recent understanding of neuropsychiatric and psychotic symptoms in AD have clarified their role as significant components of the clinical manifestation and experience of AD, developing tools that promote their assessment in a consistent, targeted and personalised manner is crucial to the promotion of early intervention, improved outcomes for the person with dementia, and reduced caregiver burden (Raphael, 2025; Rose et al., 2025).

9.4. Strengths and limitations of this thesis

Some of the main strengths of this thesis lie in the methodological approaches employed in the different studies and systematic reviews, inclusive of elements of novelty; however, some limitations should be acknowledged as well. Starting from the two systematic reviews, they were both in line with the most recent guidelines, the PRISMA framework, and they were both pre-registered on OSF to ensure transparency and reproducibility and reduce bias. However, within both reviews one potentially important limitation is that authors were not contacted to enquire about potential missing data or aspects of their methods that may have been missing from the published reports. Furthermore, while a risk of bias assessment was performed, further refinement and tailoring of the items might allow for a more precise data synthesis which considers finer methodological differences among the included studies. Despite this, it is the author's belief that the comprehensive protocols of data extraction applied, and the novel approaches to data analysis represent important strengths, which allowed synthesis of the findings in a reliable manner.

For all the studies that relied on the ADNI database, some important strengths and limitations should be considered. As outlined in chapter 1 explained, one of the main reasons for choosing to perform secondary data analysis was to ensure that the sample size of the population of interest would be large enough to allow investigation of the research questions with sufficient statistical power. This also allowed implementation of novel analyses, made possible from the large breath of data collected through the ADNI protocol. For example, within the MRI independent study (Study 2), it was possible to compare the findings of whole-brain and ROI approaches, as both types of data were available within the datasets, thus allowing suggestions to be proposed on the complementary use of these methods. Further methodological strengths of studies 3 and 4 in particular was the use of novel approaches to the analyses, which incorporated respectively an innovative approach to feature reduction (LASSO regression), and the application of the machine learning method Random Forest analysis, neither of which had been previously applied to the study of psychotic symptoms. Furthermore, in study 3, the comparison between the feature reduction approach based on LASSO and on the CFA regressions using the factors as predictors allowed the reduction of potential false positive associations, identifying clearer correlates of each psychotic manifestation, as seen above. Lastly, in both the MRI and cognitive analyses of studies 2 and 3, when investigating all sub-type groups, clear strategies of controlling for the presence of the other symptoms were applied, therefore the patterns of associations identified are specific to each thematic component. However, relying on data previously collected also included the drawback of not having flexibility to design procedures and materials, resulting in some limitations for example in relation to the neuropsychological batteries of tests available, which influenced the cognitive functions that could be evaluated in the analyses of studies 3 and 4. Furthermore, despite being a larger dataset, the sample size was still limited for example when grouping participants into specific sub-types in studies 2 and 3, or for lengthy follow-up when assessing clusters in study 1. For this reason, to maximise sample sizes, the analyses of chapters 2, 4, 6 and 7 included participants presenting with AD dementia as well as MCI; furthermore, as biomarker data was only available in a subset of the participants, this element was not used therefore the sample was inclusive of participants who were amyloid positive, amyloid negative as well as of those who did not present with this information. Future studies, should sample size allow, could benefit from using biomarker data to refine their

samples. It should also be noted as a limitation that an a priori power analysis was not undertaken, because the sample size was maximised where possible, given the use of the ADNI repository, and could not be modified in response to power calculation. However, the findings were interpreted with consideration of the observed effect estimates and confidence intervals. Furthermore, as seen in previous chapters, it is the author's belief that the frequency of the data on psychotic and neuropsychiatric symptoms using the NPI might benefit from incrementations, as the yearly collections might have resulted in missed information on the fluctuating nature of these symptomology which would be interesting to explore in the future for the development of a more precise phenomenological profile. Lastly, as mentioned in previous chapters, the ADNI database is also limited in terms of racial and cultural diversity, comprising of mostly white, highly educated people, as was also the case in the last study, with participants recruited from the researcher using Join Dementia Research. This element could be addressed in future studies as it may be relevant in relation to potential discrepancies in the attitudes towards these symptoms from both person with dementia and caregiver, based on their cultural beliefs.

With regard to study 5, it is important to consider that this was a pilot, therefore it was only possible to draw preliminary hypotheses on aspects such as potential triggers and symptoms co-occurrences that would be interesting to further explore in future studies. Other potentially relevant elements could not be investigated due to the lack of diversity within the sample, for example any gender differences with respect to caregiving attitudes, which would be interesting to address in the future. Despite this, it did have the strength of being based on a personalised approach to the development of an integrated cognitive, functional and neuropsychiatric profile, representing a first step in the direction of providing individual assessment and consequently propose targeted management strategies. Furthermore, as the research protocol was designed following Patient and Public Involvement and Engagement principles, the users' priorities were central to the project, and importantly their inputs helped outline future directions to advance the research of neuropsychiatric and psychotic assessment which incorporate the users' desired functionalities and outcomes.

9.5. Concluding remarks

In conclusion, this thesis has advanced the understanding of psychotic symptoms through a variety of different novel approaches, and importantly, it has proposed an integrated model which considers the contribution of several, inter-related variables in the manifestation of these symptoms. Furthermore, it has tested the use of novel methodological approaches to the study of psychotic symptoms, integrating elements of data science to healthcare research, aligning to the prospect that in order to effectively understand complex phenomena it is necessary to consider the application of complex models. Lastly, it has developed and piloted a novel approach to the monitoring of psychotic and neuropsychiatric symptoms, which considers their fluctuating nature and the relevance of important variables such as potential triggers and symptom co-occurrences, to achieve a personalised assessment.

All of these elements which have been the focus of this programme of research have the potential to inform research and clinical contexts on the potential markers of psychotic symptoms, thus contributing to the development of targeted management and treatment strategies.

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Appendix A

Supplementary Figures and Tables of additional (longitudinal) analyses presented in chapter 2 (Study 1)

Figure A1

MMSE scores on the total sample, MCI, and AD samples

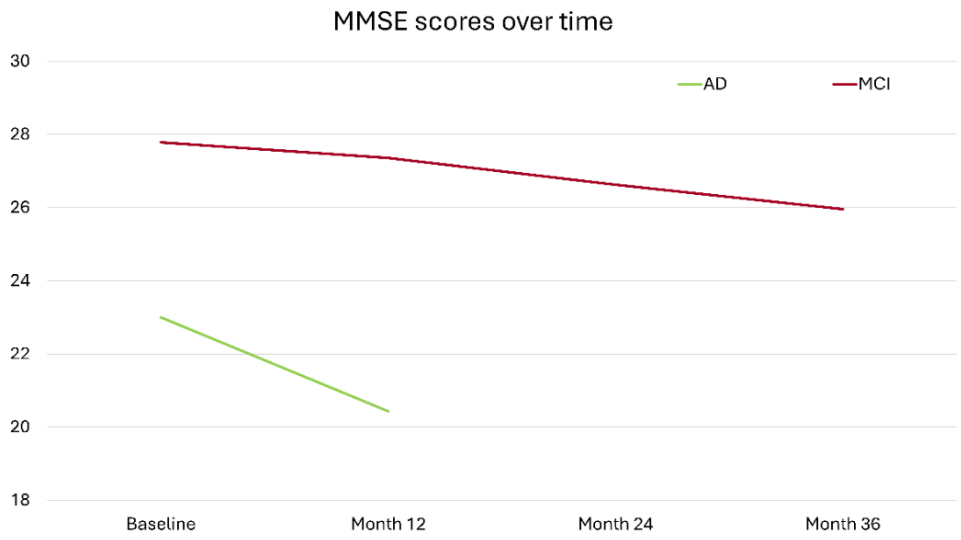


Table A1

Participants information

Sample Size	Age (at baseline)	Gender	Education	MMSE (at baseline)
147 AD	*M*=74.51 *SD*=7.94	Female=57 Male=90	*M*=15.76 *SD*=2.60	*M*=23.00 *SD*=2.29
190 MCI	*M*=71.24 *SD*=7.14	Female=82 Male=108	*M*=16.20 *SD*=2.67	*M*=27.78 *SD*=1.88

Notes. Sample sizes do not change over time as the same sets of participants are tracked. Abbreviations: M = mean, SD = standard deviation.

Table A2

Prevalence of neuropsychiatric symptoms across time

Symptom	Group	Baseline	Month 12	Month 24	Month 36
Delusions	AD	8.9%	17.0%	-	-
	MCI at Bl	2.1%	2.6%	4.2%	4.2%
Hallucinations	AD	6.2%	7.4%	-	-
	MCI at Bl	1.0%	1.0%	3.6%	6.3%
Agitation	AD	31.3%	30.6%	-	-
	MCI at Bl	15.7%	18.4%	25.7%	26.3%
Depression	AD	38.7%	39.4%	-	-
	MCI at Bl	33.1%	32.1%	33.1%	31.0%
Anxiety	AD	28.5%	36.0%	-	-
	MCI at Bl	15.2%	19.4%	21.0%	21.5%
Elation	AD	3.4%	4.7%	-	-
	MCI at Bl	1.5%	1.0%	3.6%	2.1%
Apathy	AD	44.8%	48.9%	-	-
	MCI at Bl	17.8%	24.7%	26.3%	29.4%
Disinhibition	AD	20.4%	18.3%	-	-
	MCI at Bl	11.0%	11.0%	12.6%	16.8%
Irritability	AD	34.0%	37.4%	-	-
	MCI at Bl	25.2%	28.9%	31.0%	32.1%
Aberrant Motor Behaviour	AD	16.3%	25.8%	-	-
	MCI at Bl	2.6%	5.2%	7.3%	10.0%
Sleep Disorder	AD	18.3%	17.6%	-	-
	MCI at Bl	26.3%	25.7%	31.5%	28.9%
Appetite Disorder	AD	25.1%	31.9%	-	-
	MCI at Bl	9.4%	15.7%	20.0%	15.2%

Notes. The percentages are reported to 1 decimal place. Data was only reported for the time points used at each group (AD baseline and m12, MCI baseline, m12, m24 and m36). *Abbreviations*. Bl = baseline.

Table A3

Average positive scores of neuropsychiatric symptoms across time

Symptom	Group	Baseline	Month 12	Month 24	Month 36
Delusions	AD	4.53	4.60	-	-
	MCI at Bl	3.00	2.00	4.37	3.12
Hallucinations	AD	2.55	3.54	-	-
	MCI at Bl	3.50	1.00	3.28	1.75
Agitation	AD	3.08	3.22	-	-
	MCI at Bl	2.90	2.54	3.36	3.10
Depression	AD	2.38	2.75	-	-
	MCI at Bl	1.74	2.50	2.68	2.59
Anxiety	AD	2.85	2.94	-	-
	MCI at Bl	3.20	3.16	3.55	3.17
Elation	AD	3.20	5.28	-	-
	MCI at Bl	2.66	1.50	2.85	3.25
Apathy	AD	3.74	4.58	-	-
	MCI at Bl	2.97	4.08	4.10	4.23
Disinhibition	AD	2.33	3.14	-	-
	MCI at Bl	2.57	2.23	2.04	3.12
Irritability	AD	2.86	3.38	-	-
	MCI at Bl	2.75	3.09	2.83	3.39
Aberrant Motor Behaviour	AD	4.04	4.84	-	-
	MCI at Bl	4.60	3.50	4.00	4.52
Sleep Disorder	AD	3.40	4.46	-	-
	MCI at Bl	4.18	4.26	4.30	4.52
Appetite Disorder	AD	4.97	5.17	-	-
	MCI at Bl	4.33	4.60	4.97	4.51

Notes. The score reported here are derived from the Total Score (range 1-12) per each subscale of each Neuropsychiatric Symptom, which is calculated multiplying frequency scores (range 1-4) and severity scores (range 1-3). The average reported do not include the participants who scored 0, therefore only reflect the severity of the symptom within the percentage of participant who scored positively at that time point. Data was only reported for the time points used at each group (AD baseline and m12; MCI baseline, m12, m24 and m36). *Abbreviations*. Bl = baseline.

Table A4

Average scores of neuropsychiatric symptoms across time including zero

Symptom	Group	Baseline	Month 12	Month 24	Month 36
Delusions	AD	0.40	0.78	-	-
	MCI at Bl	0.06	0.05	0.18	0.13
Hallucinations	AD	0.15	0.26	-	-
	MCI at Bl	0.03	0.01	0.12	0.11
Agitation	AD	0.96	0.98	-	-
	MCI at Bl	0.45	0.46	0.86	0.81
Depression	AD	0.92	1.08	-	-
	MCI at Bl	0.57	0.80	0.88	0.80
Anxiety	AD	0.81	1.06	-	-
	MCI at Bl	0.48	0.61	0.74	0.68
Elation	AD	0.10	0.25	-	-
	MCI at Bl	0.04	0.01	0.10	0.06
Apathy	AD	1.68	2.24	-	-
	MCI at Bl	0.53	1.01	1.07	1.24
Disinhibition	AD	0.47	0.57	-	-
	MCI at Bl	0.28	0.24	0.25	0.52
Irritability	AD	0.97	1.26	-	-
	MCI at Bl	0.69	0.89	0.87	1.08
Aberrant Motor Behaviour	AD	0.65	1.25	-	-
	MCI at Bl	0.12	0.18	0.29	0.45
Sleep Disorder	AD	0.62	0.78	-	-
	MCI at Bl	1.10	1.10	1.35	1.31
Appetite Disorder	AD	1.25	1.65	-	-
	MCI at Bl	0.41	0.72	0.99	0.68

Notes. The score reported here are derived from the Total Score including the participants who scored 0, therefore reflect the severity of the symptoms at each time point within all participants (range 0-12). Data was only reported for the time points used at each group (AD baseline and m12; MCI baseline, m12, m24 and m36). *Abbreviations*. Bl = baseline.

Table A5

PCA and FA on the AD samples at all time points available

		PRINCIPAL COMPONENT ANALYSIS				FACTOR ANALYSIS			
Time point	**Variance**	**C 1**	**C 2**	**C 3**	**C 4**	**F 1**	**F 2**	**F 3**	**F 4**
Baseline	59%	Agitation Depression Anxiety Irritability Amb	Elation Disinhibition	Apathy Sleep Appetite	Delusions Hallucinations	Agitation Depression Anxiety Irritability	Elation Disinhibition	Hallucinations	Apathy
Month 12	58%	Delusions Agitation Elation Disinhibition Irritability	Hallucinations Apathy Amb	Depression Anxiety	Sleep Appetite	Delusions Agitation Irritability	Hallucinations	Depression Anxiety	Apathy Sleep Appetite

Notes. The factors are reported as extracted using principal axis factoring extraction method, and direct oblimin rotation method; the promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the direct oblimin method. *Abbreviations*. Amb = aberrant motor behaviour; C = component; F = factor.

Table A6

PCA and FA on the MCI samples at all time points available

		PRINCIPAL COMPONENT ANALYSIS					FACTOR ANALYSIS				
Time point	**Variance**	**C 1**	**C 2**	**C 3**	**C 4**	**C 5**	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**
Baseline	55%	Agitation Irritability	Delusions Depression	Anxiety Elation Disinhibition Amb	Sleep Appetite		Anxiety Elation Apathy Disinhibition	Delusions Depression	Sleep Appetite	Agitation Irritability	
Month 12	54%	Depression Apathy Appetite	Agitation Disinhibition Irritability Amb	Anxiety Elation Sleep	Delusions Hallucinations		Apathy Appetite	Agitation Disinhibition Amb	Depression Anxiety	Irritability	
Month 24	56%	Hallucinations Agitation Anxiety Irritability	Depression Apathy	Elation Disinhibition Amb	Sleep Appetite		Depression Apathy Appetite	Agitation Irritability	Amb	Hallucinations Anxiety	
Month 36	66%	Agitation Irritability	Depression Appetite Sleep	Hallucinations Anxiety Amb	Elation Disinhibition	Delusions Apathy	Depression Appetite	Elation Disinhibition	Hallucinations Anxiety	Agitation Irritability	Delusions

Notes. The factors are reported as extracted using principal axis factoring extraction method, and direct oblimin rotation method; the promax rotation method was also performed to confirm the co-occurrence of the factors, however, when the order of the factors differed, they were reported according to the direct oblimin method. *Abbreviations*. Amb = aberrant motor behaviour; C = component; F = factor.

Appendix B

Supplementary material for the systematic review of chapter 3

Joanne Briggs Institute Risk of Bias Assessment

JBI critical appraisal checklist for analytical cross-sectional studies (also used in chapter 5) to assess risk of bias of the studies included in the systematic reviews

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JBI CRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS SECTIONAL STUDIES

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Comments (Including reason for exclusion)

_____

_____

EXPLANATION OF ANALYTICAL CROSS SECTIONAL STUDIES CRITICAL APPRAISAL

Answers: Yes, No, Unclear or Not/Applicable

1. Were the criteria for inclusion in the sample clearly defined?

The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Were the study subjects and the setting described in detail?

The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were objective, standard criteria used for measurement of the condition?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Table B1

Summary of the papers which reported significant findings

Symptom group	MRI (GM, regional)	MRI (GM, whole brain - voxels)	MRI (WM)	MRI (WMH)	CT (GM and WM)	PET	SPECT	fMRI
Delusions	Nowrangi et al., 2021 Schroeter et al., 2020 Tetrault et al., 2020 Whitehead et al., 2012	Boublay et al., 2020 Bruen et al., 2008 Fischer et al. 2016 Jedidi et al. 2015 Nakaaki et al., 2013 (A) Qian et al., 2019 (A) Serra et al., 2010 Tagawa et al., 2014 Ting et al., 2015	Lee et al. 2006 Palmqvist et al., 2011 Nakaaki et al., 2013 (B)	Anor et al., 2017 Anor et al., 2021 Barber et al., 1999 Ogawa et al., 2013	Forstl et al., 1991 Geroldi et al., 2000 Palmqvist et al., 2011	Hirono et al., 1998 Jedidi et al. 2015 Mentis et al. 1995 Reeves et al., 2009 Schroeter et al., 2020 Sultzer et al., 2003 Sultzer et al., 2014 Tissot et al., 2021	Fukuhara et al. 2001 Kotrla et al. 1995 Lee et al., 2009 Matsuoka et al. 2010 Nakano et al., 2005 Nakatsuka et al., 2013 Nomura et al., 2012 Ponton et al., 1995 Shanks and Venneri, 2002 Staff et al., 1999 Staff et al., 2000 Starkenstein et al., 1994 Venneri et al., 2000	Qian et al., 2019 (B) Serra et al., 2020
Hallucinations	Donovan et al., 2014	Blanc et al., 2014 Boublay et al., 2020 Holroyd, Shepherd and Downs, 2000	Blanc et al., 2014 Palmqvist et al., 2011	Anor et al., 2021 Barber et al., 1999 Lin, Yu and Pai 2006	Palmqvist et al., 2011	Blanc et al., 2014 Tissot et al., 2021 Lopez et al., 2001	Kotrla et al., 1995 Mori et al., 2006	

Symptom group	MRI (GM, regional)	MRI (GM, whole brain - voxels)	MRI (WM)	MRI (WMH)	CT (GM and WM)	PET	SPECT	fMRI
Psychotic cluster	D'Antonio et al., 2021 Jeong et al., 2021 Lee et al., 2019 Lee et al., 2021 McLachlan et al., 2018 Misquitta et al., 2020 Ramusino et al., 2021 Rafii et al., 2014 Siafarikas et al., 2021	D'Antonio et al., 2019 Lee et al., 2016 Makovak et al., 2016		Misquitta et al., 2020 Sultzer et al., 2002	Ramusino et al., 2021	Cappelletto et al., 2021 Koppel et al., 2014 Lopez et al., 2001 Sultzer et al., 1995	Banno et al., 2014 Mega et al., 2000 Moran et al., 2008	

Table B2

Summary of the papers which reported non-significant findings

Symptom group	MRI (GM, regional)	MRI (GM, whole brain - voxels)	MRI (WMH)	PET	fMRI
Delusions	Garcia-Alberca et al., 2019 Horinek et al., 2006 Jaramillo-Jimenez et al., 2021 Moon et al., 2014 Staekenborg et al., 2008 Tascone et al., 2017	Tascone et al., 2017	Berlow et al., 2010 Garcia-Alberca et al., 2019 Staekenborg et al., 2008		Lee, Kim and Lee, 2020 Serra et al., 2018
Hallucinations	Garcia-Alberca et al., 2019 Horinek et al., 2006 Jaramillo-Jimenez et al., 2021 Moon et al., 2014 Staekenborg et al., 2008 Tascone et al., 2017 Tetrault et al., 2020 Wang et al., 2020	Serra et al., 2010 Tascone et al., 2017	Garcia-Alberca et al., 2019 Lee et al., 2006 Ogawa et al., 2013 Staekenborg et al., 2008	Hirono et al., 1998	Lee, Kim and Lee, 2020 Serra et al., 2018
Psychotic cluster		Hayata et al., 2015		Santosh et al., 2009 Yasuno, Minami and Hattori, 2020	Balthazar et al., 2014

Table B3

Peak clusters of coordinates derived from the meta-analysis on fourteen studies on delusions

Cluster ID	X	Y	Z	Peak Statistic (z)	Cluster Size (mm3)	Label (MNI structural atlas)
1	28	12	-10	3.966863	4528	R Putamen (27%)
1a	32	22	-10	3.966863		R Insula (60%)
1b	26	14	-2	3.082144		R Putamen (100%)
1c	38	26	-8	2.081893		R Frontal Lobe (40%)
2	42	8	44	3.966863	5720	R Frontal Lobe (60%)
2a	40	14	38	3.082144		R Frontal Lobe (28%)
2b	50	14	38	3.082144		R Frontal Lobe (78%)
2c	34	4	46	2.081893		R Frontal Lobe (10%)
3	-40	4	4	3.082144	8392	L Insula (52%)
3a	-34	8	14	3.082144		L Insula (34%)
3b	-42	16	6	2.081893		L Frontal Lobe (62%)
3c	-40	-4	2	2.081893		L Insula (54%)
4	-34	34	-8	3.082144	1920	L Frontal Lobe (18%)
4a	-40	40	-8	2.081893		L Frontal Lobe (35%)
4b	-36	28	-14	2.081893		L Frontal Lobe (36%)
4c	-40	34	-2	2.081893		L Frontal Lobe (30%)
5	36	36	-4	3.082144	5784	R Frontal Lobe (14%)
5a	42	38	-12	3.082144		R Frontal Lobe (81%)
5b	42	44	-6	3.082144		R Frontal Lobe (28%)
5c	32	48	-6	2.081893		R Frontal Lobe (12%)
6	48	-6	18	3.082144	2088	R Parietal Lobe (42%)
6a	44	-12	12	2.081893		R Parietal Lobe (65%)
6b	46	-8	24	2.081893		R Parietal Lobe (3%)
6c	52	0	18	2.081893		R Frontal Lobe (5%)

Cluster ID	X	Y	Z	Peak Statistic (z)	Cluster Size (mm3)	Label (MNI structural atlas)
7	24	-32	2	2.081893	8	R Thalamus (1%)
8	26	-32	4	2.081893	8	R Occipital (50%)
9	26	-30	2	2.081893	8	R Occipital (45%)
10	34	-72	46	2.081893	152	R Parietal Lobe (83%)
11	34	-12	18	2.081893	8	R Insula (34%)
12	36	-8	20	2.081893	8	R Insula (31%)
13	38	-78	-8	2.081893	16	R Occipital Lobe (54%)
14	-50	-34	-22	2.081893	288	L Temporal Lobe (93%)
15	24	-34	4	2.081893	8	R Thalamus (1%)
16	46	0	-34	2.081893	272	R Temporal Lobe (65%)
17	44	52	2	2.081893	8	R Frontal Lobe (86%)
18	46	44	2	2.081893	8	R Frontal Lobe (81%)
19	46	50	0	2.081893	8	R Frontal Lobe (85%)
20	54	-20	30	2.081893	320	R Parietal Lobe (64%)
21	50	-16	20	2.081893	208	R Parietal Lobe (63%)
22	48	30	26	2.081893	8	R Frontal Lobe (66%)
23	52	36	-4	2.081893	704	R Frontal Lobe (76%)
24	50	44	0	2.081893	16	R Frontal Lobe (93%)
25	38	24	18	2.081893	8	R Frontal Lobe (8%)
26	42	28	22	2.081893	464	R Frontal Lobe (65%)
27	20	-60	-18	2.081893	704	R Cerebellum (95%)
28	52	-12	24	2.081893	8	R Parietal Lobe (13%)
29	-40	-38	-26	2.081893	576	L Temporal Lobe (90%)
30	-42	-66	10	2.081893	48	L Occipital Lobe (66%)
31	-32	-72	0	2.081893	104	L Occipital Lobe (9%)
32	-30	-54	36	2.081893	368	L Parietal Lobe (44%)
33	-26	-42	-8	2.081893	872	L Occipital Lobe (2%)

Cluster ID	X	Y	Z	Peak Statistic (z)	Cluster Size (mm3)	Label (MNI structural atlas)
34	-28	26	-16	2.081893	592	L Frontal Lobe (38%)
35	-22	36	28	2.081893	320	L Frontal Lobe (4%)
36	-20	-46	34	2.081893	1232	L Cerebral WM (100%) *
37	-18	-50	42	2.081893	16	L Parietal Lobe (2%)
38	-14	-10	68	2.081893	1984	L Frontal Lobe (54%)
39	18	-38	-6	2.081893	152	R Parietal Lobe (12%)
40	-16	26	-20	2.081893	432	L Frontal Lobe (63%)
41	-12	-6	44	2.081893	8	L Frontal Lobe (63%)
42	-2	-68	30	2.081893	704	L Parietal Lobe (79%)
43	8	40	26	2.081893	2424	R Frontal Lobe (91%)
44	2	-34	-4	2.081893	8	R Brainstem (80%) *
45	10	60	0	2.081893	2424	R Frontal Lobe (71%)
46	4	-80	34	2.081893	8	R Occipital Lobe (49%)
47	4	-34	-2	2.081893	8	R Brainstem (58%) *
48	8	-78	34	2.081893	8	R Occipital Lobe (73%)
49	14	12	64	2.081893	1056	R Frontal Lobe (56%)
50	18	-58	10	2.081893	1120	R Parietal Lobe (23%)
51	-14	-6	42	2.081893	8	L Frontal Lobe (21%)
52	52	-10	30	2.081893	8	R parietal Lobe (12%)

Notes. Coordinates are expressed in MNI space. No correction was applied; clusters are significant at z >= 1.64 (equivalent to $p<.05$).
*the MNI structural atlas was not available on this coordinate, so the label was derived from the Harvard-Oxford Subcortical Structural Atlas.

Appendix C

Supplementary tables of chapter 4 (Study 2)

Table C1

Regions selected from FreeSurfer for the Region of Interest analyses, based on findings from systematic review in chapter 3

Region	Right	Left
Anterior Cingulate Cortex	ST113,73TA,CV,SA	ST14,54TA,CV,SA
Posterior Cingulate Cortex	ST109TA,CV,SA	ST50TA,CV,SA
Superior Frontal	ST115TA,CV,SA	ST56TA,CV,SA
Medial Frontal	ST114,74TA,CV,SA	ST15,55TA,CV,SA
Inferior Frontal Opercularis	ST104TA,CV,SA	ST45TA,CV,SA
Inferior Frontal Orbitalis	ST105TA,CV,SA	ST46TA,CV,SA
Inferior Frontal Triangularis	ST106TA,CV,SA	ST47TA,CV,SA
Precuneus	ST111TA,CV,SA	ST52TA,CV,SA
Insula	ST130TA,CV,SA	ST129TA,CV,SA
Orbitofrontal	ST95,98TA,CV,SA	ST36,39TA,CV,SA
Superior Temporal	ST117TA,CV,SA	ST58TA,CV,SA
Medial Temporal	ST99TA,CV,SA	ST40TA,CV,SA
Inferior Temporal	ST91TA,CV,SA	ST32TA,CV,SA
Putamen	ST112SV	ST53SV
Parahippocampus	ST103TA,CV,SA	ST44TA,CV,SA
Entorhinal Cortex	ST83TA,CV,SA	ST24TA,CV,SA
Cerebellum	ST76SV,77SV	ST17SV
Superior Parietal	ST116TA,CV,SA	ST57TA,CV,SA
Inferior Parietal	ST90TA,CV,SA	ST31TA,CV,SA
Occipital	ST94TA,CV,SA	ST35TA,CV,SA
Lingual	ST97TA,CV,SA	ST38TA,CV,SA

Abbreviations. CV = cortical volume; TA = cortical thickness; SA = surface area; SV = sub-cortical volume.

Table C2

Non-significant associations of demographic variables between groups of participants with and without psychotic symptoms (divided per group)

Variable	Test	Statistic	df	*p*	Effect Size
		Psychosis			
Age	t	0.33	137.92	.739	0.06
Education	t	1.18	137.87	.241	0.2
MMSE	t	-1.3	135.02	.194	-0.22
MOCA	t	-1.9	134.89	.06	-0.32
NPI	t	0.61	106.08	.545	0.1
Gender	Chi-square	2.34	1	.126	0.13
Disease Stage	Chi-square	3.4	1	.065	0.16
APOE4	Chi-square	0.74	1	.388	0.08
		Delusions			
Age	t	0.62	75.99	.537	0.14
Education	t	1.51	75.78	.135	0.34
MMSE	t	-0.26	72.42	.797	-0.06
MOCA	t	-0.37	73.58	.713	-0.08
NPI	t	-0.04	67.08	.971	-0.01
Gender	Chi-square	0.05	1	.821	0.03
Disease Stage	Chi-square	0.08	1	.784	0.03
APOE4	Chi-square	0	1	1	0
		Hallucinations			
Age	t	-0.4	31.29	.692	-0.13
Education	t	0.63	33.56	.536	0.2
MMSE	t	1.06	35.86	.297	0.34
MOCA	t	-0.54	30.72	.593	-0.18
NPI	t	-0.01	30.45	.99	0
Gender	Chi-square	0.11	1	.746	0.05
Disease Stage	Chi-square	0.54	1	.461	0.12
APOE4	Fisher exact			.448	
		Misidentification			
Age	t	-0.45	43.94	.656	-0.13
Education	t	0.44	40.07	.659	0.13
MMSE	t	1.52	40.99	.136	0.45
MOCA	t	-0.04	43.2	.965	-0.01
NPI	t	0.36	28.34	.723	0.11
Gender	Chi-square	0.35	1	.555	0.09
Disease Stage	Chi-square	1.08	1	.3	0.15
APOE4	Fisher exact			.226	
		Paranoia			
Age	t	0.16	35.95	.873	0.05
Education	t	1.2	34.75	.238	0.39

Variable	Test	Statistic	df	*p*	Effect Size
MMSE	t	0.58	35.73	.568	0.19
MOCA	t	0.37	35.45	.713	0.12
NPI	t	0.3	29.24	.77	0.1
Gender	Chi-square	0.96	1	.328	0.16
Disease Stage	Fisher exact			.405	
APOE4	Fisher exact			.183	
		Delusion of Theft			
Age	t	-0.11	29.99	.914	-0.04
Education	t	0.69	28.98	.498	0.24
MMSE	t	0.55	29.87	.585	0.2
MOCA	t	0	28.85	1	0
NPI	t	0.57	24.66	.577	0.2
Gender	Chi-square	0.51	1	.476	0.13
Disease Stage	Fisher exact			.654	
APOE4	Fisher exact			.097	

Table C3

Non-significant brain areas of the ROI approach

FreeSurfer brain areas	Non-significant findings
	Psychosis
ST105CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.050
ST58CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.054
ST129SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.106
ST14SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.113
ST58TA	OR = 0.28 [95% CI 0.06-1.33], p = 0.117
ST35TA	OR = 0.14 [95% CI 0.01-1.63], p = 0.121
ST73SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.142
ST32CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.145
ST40CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.154
ST55CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.159
ST44SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.161
ST130TA	OR = 3.25 [95% CI 0.64-17.78], p = 0.161
ST50SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.173
ST40TA	OR = 0.38 [95% CI 0.08-1.61], p = 0.195
ST109TA	OR = 4.00 [95% CI 0.47-37.58], p = 0.212
ST54TA	OR = 2.50 [95% CI 0.59-11.12], p = 0.217
ST40SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.220
ST54SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.229
ST32TA	OR = 0.40 [95% CI 0.09-1.75], p = 0.229
ST73CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.241
ST35CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.265
ST58SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.265
ST54CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.266
ST115SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.270
ST98CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.274
ST46CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.276
ST97TA	OR = 0.28 [95% CI 0.03-2.84], p = 0.285
ST95SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.293
ST44CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.298
ST56SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.305
ST113SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.306
ST94TA	OR = 0.31 [95% CI 0.03-2.87], p = 0.308
ST50TA	OR = 3.11 [95% CI 0.35-29.73], p = 0.314
ST56CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.323
ST50CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.327
ST46SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.328
ST14CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.331
ST94CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.338
ST91CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.338
ST105SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.340

FreeSurfer brain areas	Non-significant findings
ST83SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.351
ST115CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.355
ST106TA	OR = 2.93 [95% CI 0.30-31.41], p = 0.358
ST32SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.358
ST55SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.363
ST116CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.367
ST57TA	OR = 0.41 [95% CI 0.06-2.92], p = 0.379
ST98SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.395
ST57SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.406
ST103SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.409
ST129CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.412
ST113TA	OR = 1.67 [95% CI 0.48-6.07], p = 0.421
ST14TA	OR = 1.62 [95% CI 0.49-5.61], p = 0.434
ST130SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.449
ST95TA	OR = 0.45 [95% CI 0.05-3.58], p = 0.454
ST74SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.455
ST99SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.464
ST105TA	OR = 0.55 [95% CI 0.10-2.86], p = 0.476
ST111SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.476
ST91TA	OR = 0.59 [95% CI 0.13-2.64], p = 0.489
ST103CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.493
ST45TA	OR = 2.28 [95% CI 0.21-26.17], p = 0.502
ST55TA	OR = 0.48 [95% CI 0.05-4.42], p = 0.516
ST129TA	OR = 1.67 [95% CI 0.34-8.35], p = 0.527
ST38CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.529
ST73TA	OR = 0.64 [95% CI 0.15-2.60], p = 0.537
ST113CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.543
ST91SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.543
ST112SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.549
ST83CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.573
ST111CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.573
ST106SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.597
ST38TA	OR = 1.84 [95% CI 0.18-19.02], p = 0.605
ST90SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.608
ST52TA	OR = 0.62 [95% CI 0.09-4.25], p = 0.624
ST114CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.629
ST130CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.631
ST31TA	OR = 0.64 [95% CI 0.10-3.97], p = 0.631
ST94SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.633
ST74TA	OR = 1.59 [95% CI 0.24-10.91], p = 0.635
ST57CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.645
ST114TA	OR = 0.59 [95% CI 0.06-5.84], p = 0.649
ST47TA	OR = 0.61 [95% CI 0.07-5.27], p = 0.650
ST74CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.655
ST77SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.657

FreeSurfer brain areas	Non-significant findings
ST52CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.659
ST36SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.666
ST83TA	OR = 1.16 [95% CI 0.59-2.32], p = 0.667
ST99CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.669
ST97CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.669
ST116SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.676
ST44TA	OR = 0.81 [95% CI 0.30-2.15], p = 0.677
ST15SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.678
ST31SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.690
ST15TA	OR = 0.71 [95% CI 0.12-4.14], p = 0.705
ST76SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.722
ST117CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.725
ST109CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.734
ST45CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.737
ST36CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.740
ST90CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.741
ST104CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.748
ST24TA	OR = 1.10 [95% CI 0.55-2.23], p = 0.787
ST52SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.792
ST35SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.795
ST116TA	OR = 1.26 [95% CI 0.20-7.88], p = 0.803
ST45SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.807
ST95CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.808
ST39CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.814
ST47CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.816
ST36TA	OR = 1.27 [95% CI 0.16-10.47], p = 0.820
ST31CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.823
ST56TA	OR = 1.23 [95% CI 0.17-9.12], p = 0.838
ST24SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.844
ST117SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.867
ST90TA	OR = 0.87 [95% CI 0.17-4.49], p = 0.870
ST115TA	OR = 1.17 [95% CI 0.16-8.94], p = 0.878
ST104TA	OR = 1.18 [95% CI 0.14-9.99], p = 0.879
ST97SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.882
ST39TA	OR = 0.87 [95% CI 0.14-5.44], p = 0.883
ST24CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.904
ST15CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.904
ST39SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.909
	Delusions
ST105CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.028
ST57SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.042
ST31SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.044
ST57CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.049
ST39SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.091
ST31CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.098

FreeSurfer brain areas	Non-significant findings
ST116CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.101
ST15CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.142
ST117SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.143
ST76SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.147
ST39CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.153
ST83SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.154
ST15SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.156
ST83CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.168
ST17SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.196
ST112SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.200
ST14TA	OR = 3.30 [95% CI 0.56-23.08], p = 0.201
ST91TA	OR = 0.26 [95% CI 0.03-1.99], p = 0.205
ST38CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.207
ST58SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.209
ST38TA	OR = 6.82 [95% CI 0.33-167.62], p = 0.221
ST114SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.242
ST53SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.256
ST90CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.267
ST116SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.282
ST98TA	OR = 4.02 [95% CI 0.30-67.68], p = 0.304
ST50TA	OR = 5.60 [95% CI 0.21-172.23], p = 0.309
ST111CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.313
ST52CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.322
ST113SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.331
ST94SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.338
ST109TA	OR = 4.00 [95% CI 0.25-79.71], p = 0.340
ST111SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.353
ST77SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.421
ST90SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.425
ST52SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.426
ST130CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.432
ST114CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.434
ST103CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.436
ST103SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.443
ST83TA	OR = 0.71 [95% CI 0.28-1.72], p = 0.445
ST115CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.476
ST99TA	OR = 0.51 [95% CI 0.07-3.45], p = 0.489
ST95SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.489
ST97TA	OR = 0.35 [95% CI 0.02-7.32], p = 0.498
ST56TA	OR = 2.33 [95% CI 0.19-31.02], p = 0.510
ST113CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.511
ST44SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.519
ST24TA	OR = 0.73 [95% CI 0.27-1.90], p = 0.521
ST95TA	OR = 0.41 [95% CI 0.02-6.27], p = 0.526
ST105SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.527

FreeSurfer brain areas	Non-significant findings
ST73SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.530
ST117CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.533
ST115SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.537
ST98CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.539
ST116TA	OR = 2.01 [95% CI 0.22-20.28], p = 0.541
ST113TA	OR = 1.74 [95% CI 0.29-11.08], p = 0.546
ST129CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.549
ST54TA	OR = 1.75 [95% CI 0.27-11.84], p = 0.556
ST35TA	OR = 0.38 [95% CI 0.01-9.90], p = 0.559
ST129TA	OR = 1.89 [95% CI 0.21-18.03], p = 0.574
ST94CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.575
ST56CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.579
ST91CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.611
ST58TA	OR = 0.61 [95% CI 0.08-4.34], p = 0.618
ST117TA	OR = 0.60 [95% CI 0.07-4.52], p = 0.621
ST35SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.623
ST58CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.625
ST106TA	OR = 2.06 [95% CI 0.10-51.98], p = 0.642
ST47TA	OR = 0.52 [95% CI 0.03-9.37], p = 0.654
ST32TA	OR = 0.64 [95% CI 0.09-4.61], p = 0.658
ST130TA	OR = 1.57 [95% CI 0.21-12.62], p = 0.662
ST40TA	OR = 0.66 [95% CI 0.09-4.37], p = 0.663
ST114TA	OR = 0.53 [95% CI 0.03-9.91], p = 0.670
ST24SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.671
ST36SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.685
ST45TA	OR = 2.03 [95% CI 0.06-68.85], p = 0.686
ST46CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.689
ST46TA	OR = 0.66 [95% CI 0.08-5.28], p = 0.691
ST57TA	OR = 0.60 [95% CI 0.05-7.50], p = 0.692
ST99SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.707
ST38SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.710
ST55SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.711
ST39TA	OR = 1.59 [95% CI 0.13-19.60], p = 0.713
ST111TA	OR = 1.53 [95% CI 0.15-15.92], p = 0.714
ST54SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.721
ST94TA	OR = 0.61 [95% CI 0.04-9.30], p = 0.721
ST47CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.722
ST109CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.732
ST56SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.737
ST115TA	OR = 1.52 [95% CI 0.13-18.84], p = 0.740
ST104CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.744
ST106CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.748
ST104TA	OR = 1.50 [95% CI 0.10-22.56], p = 0.765
ST90TA	OR = 1.35 [95% CI 0.19-10.15], p = 0.766
ST73CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.769

FreeSurfer brain areas	Non-significant findings
ST36CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.770
ST103TA	OR = 0.79 [95% CI 0.16-3.85], p = 0.770
ST15TA	OR = 1.38 [95% CI 0.16-12.31], p = 0.771
ST32SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.784
ST50CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.785
ST47SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.790
ST98SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.798
ST32CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.805
ST55CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.805
ST44CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.821
ST14CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.822
ST44TA	OR = 1.15 [95% CI 0.31-4.36], p = 0.835
ST52TA	OR = 1.31 [95% CI 0.10-18.47], p = 0.838
ST45CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.846
ST74TA	OR = 1.23 [95% CI 0.13-11.79], p = 0.854
ST45SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.868
ST14SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.872
ST24CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.875
ST97SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.876
ST74SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.877
ST40CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.886
ST109SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.886
ST40SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.887
ST55TA	OR = 0.82 [95% CI 0.04-18.12], p = 0.902
ST50SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.921
ST35CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.921
	Hallucinations
ST112SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.032
ST109SA	OR = 1.01 [95% CI 1.00-1.01], p = 0.038
ST130CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.044
ST113CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.047
ST109CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.057
ST130SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.057
ST53SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.073
ST73TA	OR = 0.06 [95% CI 0.00-0.98], p = 0.073
ST17SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.079
ST95SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.082
ST113SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.093
ST31SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.097
ST54TA	OR = 16.51 [95% CI 0.79-763.42], p = 0.100
ST77SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.101
ST39SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.106
ST35SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.108
ST95CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.110
ST38CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.123

FreeSurfer brain areas	Non-significant findings
ST76SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.125
ST36CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.139
ST103CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.148
ST83TA	OR = 3.72 [95% CI 0.67-31.07], p = 0.166
ST40SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.168
ST97CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.173
ST50CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.174
ST36SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.174
ST24TA	OR = 2.80 [95% CI 0.66-14.37], p = 0.180
ST105TA	OR = 13.23 [95% CI 0.34-936.96], p = 0.190
ST117SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.191
ST90SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.196
ST114SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.219
ST24CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.223
ST98TA	OR = 0.06 [95% CI 0.00-4.18], p = 0.223
ST38SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.225
ST47SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.231
ST58TA	OR = 0.09 [95% CI 0.00-3.64], p = 0.231
ST52SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.236
ST73SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.242
ST90CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.248
ST74CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.250
ST50TA	OR = 10.99 [95% CI 0.21-913.64], p = 0.250
ST44TA	OR = 3.39 [95% CI 0.45-32.34], p = 0.253
ST52CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.260
ST129TA	OR = 6.89 [95% CI 0.26-280.64], p = 0.266
ST98CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.268
ST106TA	OR = 16.45 [95% CI 0.13-3457.16], p = 0.269
ST74SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.272
ST56SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.277
ST94SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.278
ST54SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.284
ST105SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.286
ST116CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.294
ST55SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.295
ST103TA	OR = 4.37 [95% CI 0.30-85.99], p = 0.296
ST35CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.297
ST94CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.300
ST54CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.304
ST104SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.321
ST117CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.321
ST39TA	OR = 0.15 [95% CI 0.00-5.84], p = 0.324
ST91SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.330
ST55TA	OR = 0.09 [95% CI 0.00-9.95], p = 0.332
ST97SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.347

FreeSurfer brain areas	Non-significant findings
ST44CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.348
ST31CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.350
ST83CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.354
ST129CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.355
ST103SA	OR = 1.01 [95% CI 0.99-1.02], p = 0.363
ST91CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.364
ST113TA	OR = 3.89 [95% CI 0.26-125.72], p = 0.369
ST99TA	OR = 4.71 [95% CI 0.17-190.10], p = 0.373
ST15CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.381
ST98SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.383
ST15SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.384
ST32SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.391
ST99CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.396
ST130TA	OR = 4.77 [95% CI 0.14-232.10], p = 0.398
ST47CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.398
ST58SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.422
ST116SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.423
ST115SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.427
ST36TA	OR = 6.29 [95% CI 0.06-827.31], p = 0.439
ST105CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.441
ST117TA	OR = 5.95 [95% CI 0.07-692.12], p = 0.442
ST114TA	OR = 0.17 [95% CI 0.00-16.90], p = 0.454
ST46TA	OR = 5.32 [95% CI 0.07-584.91], p = 0.461
ST32TA	OR = 0.31 [95% CI 0.01-6.67], p = 0.463
ST40CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.477
ST24SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.479
ST14SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.482
ST99SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.482
ST106CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.531
	Misidentification
ST130TA	OR = 31.23 [95% CI 2.02-842.15], p = 0.022
ST105TA	OR = 49.17 [95% CI 1.72-2838.06], p = 0.035
ST39SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.035
ST129TA	OR = 19.46 [95% CI 1.22-512.74], p = 0.050
ST130CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.050
ST77SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.060
ST99TA	OR = 16.36 [95% CI 1.04-448.83], p = 0.064
ST95SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.068
ST17SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.086
ST112SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.088
ST46TA	OR = 19.13 [95% CI 0.66-869.96], p = 0.101
ST24TA	OR = 2.93 [95% CI 0.85-11.67], p = 0.102
ST36TA	OR = 32.15 [95% CI 0.56-2703.13], p = 0.104
ST106TA	OR = 39.73 [95% CI 0.53-5186.84], p = 0.109
ST50TA	OR = 17.39 [95% CI 0.58-876.79], p = 0.119

FreeSurfer brain areas	Non-significant findings
ST83TA	OR = 2.81 [95% CI 0.77-11.97], p = 0.131
ST117TA	OR = 9.50 [95% CI 0.53-250.26], p = 0.143
ST94SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.154
ST36CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.157
ST76SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.160
ST111TA	OR = 11.11 [95% CI 0.40-455.03], p = 0.171
ST94CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.172
ST113CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.183
ST74TA	OR = 10.82 [95% CI 0.38-499.21], p = 0.185
ST95CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.190
ST114CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.191
ST113SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.204
ST116TA	OR = 10.18 [95% CI 0.32-487.37], p = 0.206
ST104TA	OR = 14.97 [95% CI 0.30-1679.93], p = 0.208
ST24CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.208
ST31SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.212
ST117CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.217
ST103TA	OR = 4.03 [95% CI 0.43-44.67], p = 0.232
ST47SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.235
ST114SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.236
ST73TA	OR = 0.23 [95% CI 0.02-2.39], p = 0.239
ST109CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.242
ST44TA	OR = 3.16 [95% CI 0.48-24.91], p = 0.244
ST31CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.247
ST117SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.249
ST99CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.253
ST52TA	OR = 7.67 [95% CI 0.24-332.65], p = 0.261
ST45TA	OR = 9.56 [95% CI 0.20-648.96], p = 0.265
ST83SA	OR = 0.99 [95% CI 0.98-1.00], p = 0.268
ST74SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.271
ST58SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.273
ST105CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.276
ST47CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.279
ST114TA	OR = 11.09 [95% CI 0.16-1171.00], p = 0.280
ST38TA	OR = 13.96 [95% CI 0.13-2402.02], p = 0.284
ST113TA	OR = 3.76 [95% CI 0.37-57.63], p = 0.285
ST116SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.300
ST129CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.308
ST90TA	OR = 4.15 [95% CI 0.28-76.59], p = 0.313
ST53SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.316
ST14CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.322
ST91TA	OR = 4.29 [95% CI 0.25-89.98], p = 0.323
ST44CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.327
ST111CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.328
ST98SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.334

FreeSurfer brain areas	Non-significant findings
ST97TA	OR = 9.98 [95% CI 0.10-1372.27], p = 0.335
ST109SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.337
ST36SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.354
ST56SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.356
ST91SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.360
ST91CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.367
ST52CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.371
ST32SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.387
ST35SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.403
ST115TA	OR = 5.07 [95% CI 0.12-284.83], p = 0.403
ST103SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.424
ST90CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.425
ST129SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.444
ST58CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.446
ST39TA	OR = 0.30 [95% CI 0.01-6.94], p = 0.455
ST24SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.462
ST15SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.470
ST109TA	OR = 3.59 [95% CI 0.11-139.49], p = 0.479
ST83CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.488
ST38CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.490
ST31TA	OR = 3.00 [95% CI 0.13-78.69], p = 0.491
ST40SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.497
ST115CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.497
ST55TA	OR = 4.17 [95% CI 0.07-326.39], p = 0.498
ST105SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.498
ST15CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.508
ST55CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.512
ST50SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.531
ST103CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.533
ST130SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.538
ST56CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.560
ST54TA	OR = 1.92 [95% CI 0.19-22.34], p = 0.583
ST55SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.589
ST39CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.591
ST14SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.591
ST115SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.606
ST35CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.613
ST97SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.620
ST54CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.644
ST32CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.651
ST73SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.693
ST116CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.700
ST52SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.709
ST104CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.740
ST56TA	OR = 1.84 [95% CI 0.05-81.78], p = 0.744

FreeSurfer brain areas	Non-significant findings
ST94TA	OR = 2.05 [95% CI 0.02-178.93], p = 0.748
ST57SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.769
ST45CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.769
ST15TA	OR = 1.64 [95% CI 0.06-49.65], p = 0.770
ST40CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.779
ST58TA	OR = 1.41 [95% CI 0.11-18.95], p = 0.790
ST98TA	OR = 0.61 [95% CI 0.01-38.49], p = 0.816
ST73CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.822
ST74CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.831
ST90SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.836
ST104SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.839
ST46SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.847
ST106CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.851
ST40TA	OR = 0.77 [95% CI 0.04-13.00], p = 0.852
ST50CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.852
ST14TA	OR = 0.85 [95% CI 0.10-7.22], p = 0.882
	Paranoia
ST98SA	OR = 1.01 [95% CI 1.00-1.01], p = 0.020
ST117SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.022
ST39SA	OR = 1.01 [95% CI 1.00-1.01], p = 0.022
ST105TA	OR = 0.00 [95% CI 0.00-0.64], p = 0.048
ST58SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.063
ST117CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.064
ST112SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.084
ST53SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.107
ST74SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.109
ST24SA	OR = 1.01 [95% CI 1.00-1.02], p = 0.113
ST111CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.133
ST115SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.134
ST58CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.136
ST91SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.157
ST114SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.167
ST115CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.171
ST130TA	OR = 10.17 [95% CI 0.42-378.99], p = 0.173
ST39CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.176
ST95SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.178
ST45TA	OR = 34.02 [95% CI 0.26-11288.53], p = 0.183
ST111SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.192
ST54TA	OR = 0.10 [95% CI 0.00-2.76], p = 0.203
ST130CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.209
ST98CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.213
ST52SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.223
ST103SA	OR = 0.99 [95% CI 0.98-1.00], p = 0.228
ST105CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.256
ST116TA	OR = 11.08 [95% CI 0.21-1004.19], p = 0.257

FreeSurfer brain areas	Non-significant findings
ST32SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.262
ST56SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.276
ST44TA	OR = 3.44 [95% CI 0.38-37.78], p = 0.281
ST14SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.285
ST24CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.294
ST94SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.299
ST56CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.308
ST99CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.310
ST111TA	OR = 8.00 [95% CI 0.17-628.95], p = 0.311
ST54SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.313
ST115TA	OR = 6.10 [95% CI 0.19-291.53], p = 0.321
ST36SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.326
ST74TA	OR = 5.58 [95% CI 0.19-251.57], p = 0.336
ST117TA	OR = 4.75 [95% CI 0.20-153.89], p = 0.346
ST99TA	OR = 4.35 [95% CI 0.20-114.63], p = 0.350
ST31CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.353
ST31SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.361
ST91CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.365
ST73CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.369
ST74CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.378
ST52CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.392
ST90TA	OR = 4.34 [95% CI 0.17-159.47], p = 0.392
ST114CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.393
ST17SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.394
ST104TA	OR = 6.99 [95% CI 0.09-1194.49], p = 0.413
ST129CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.415
ST36CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.422
ST98TA	OR = 0.15 [95% CI 0.00-14.00], p = 0.423
ST129SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.433
ST99SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.434
ST116CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.444
ST39TA	OR = 0.21 [95% CI 0.00-11.82], p = 0.451
ST57CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.457
ST95CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.468
ST103TA	OR = 2.82 [95% CI 0.17-54.91], p = 0.472
ST56TA	OR = 4.16 [95% CI 0.09-279.03], p = 0.474
ST105SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.475
ST113TA	OR = 0.37 [95% CI 0.02-5.62], p = 0.478
ST97TA	OR = 0.20 [95% CI 0.00-17.41], p = 0.480
ST77SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.483
ST73SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.492
ST14CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.494
ST38CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.505
ST130SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.510
ST97CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.528

FreeSurfer brain areas	Non-significant findings
ST95TA	OR = 0.22 [95% CI 0.00-24.93], p = 0.537
ST76SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.544
ST38TA	OR = 0.29 [95% CI 0.00-17.02], p = 0.544
ST106SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.548
ST113CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.575
ST57SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.585
ST94CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.588
ST58TA	OR = 2.36 [95% CI 0.10-65.02], p = 0.594
ST54CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.616
ST116SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.623
ST73TA	OR = 0.54 [95% CI 0.04-5.92], p = 0.623
ST44SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.624
ST106CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.628
ST36TA	OR = 2.69 [95% CI 0.05-204.50], p = 0.629
ST14TA	OR = 0.46 [95% CI 0.02-10.45], p = 0.630
ST44CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.630
ST47TA	OR = 0.31 [95% CI 0.00-42.12], p = 0.634
ST83SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.636
ST94TA	OR = 0.35 [95% CI 0.00-31.55], p = 0.639
ST90CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.647
ST109SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.654
ST103CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.657
ST45SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.663
ST32CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.677
ST129TA	OR = 1.99 [95% CI 0.07-64.80], p = 0.685
ST31TA	OR = 2.15 [95% CI 0.05-109.58], p = 0.687
ST90SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.726
ST40TA	OR = 0.60 [95% CI 0.03-13.18], p = 0.742
ST15SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.766
ST40SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.778
ST50TA	OR = 0.51 [95% CI 0.00-54.91], p = 0.779
ST35TA	OR = 0.50 [95% CI 0.00-71.09], p = 0.783
ST50CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.786
ST47CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.787
ST35SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.819
ST109CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.831
ST46SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.833
ST15TA	OR = 0.70 [95% CI 0.02-21.93], p = 0.835
ST97SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.844
ST55SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.850
ST24TA	OR = 0.88 [95% CI 0.21-3.67], p = 0.852
ST114TA	OR = 0.63 [95% CI 0.00-90.53], p = 0.856
ST46CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.867
ST91TA	OR = 1.32 [95% CI 0.04-39.29], p = 0.870
ST106TA	OR = 1.65 [95% CI 0.00-968.32], p = 0.874

FreeSurfer brain areas	Non-significant findings
	Delusion of theft
ST53SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.052
ST45TA	OR = 1576.32 [95% CI 1.96-10211065.61], p = 0.057
ST73SA	OR = 0.99 [95% CI 0.98-1.00], p = 0.061
ST46CV	OR = 1.00 [95% CI 0.99-1.00], p = 0.077
ST45SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.077
ST105TA	OR = 0.01 [95% CI 0.00-1.14], p = 0.082
ST74SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.099
ST56TA	OR = 45.31 [95% CI 0.56-9252.87], p = 0.113
ST57CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.123
ST104CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.139
ST46SA	OR = 0.99 [95% CI 0.99-1.00], p = 0.140
ST113CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.141
ST116TA	OR = 20.73 [95% CI 0.46-2262.25], p = 0.153
ST32TA	OR = 19.18 [95% CI 0.41-1756.18], p = 0.154
ST117SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.169
ST44SA	OR = 0.99 [95% CI 0.98-1.00], p = 0.170
ST104SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.172
ST15SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.174
ST14TA	OR = 0.14 [95% CI 0.01-2.11], p = 0.180
ST15TA	OR = 14.84 [95% CI 0.34-1122.80], p = 0.181
ST112SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.189
ST113TA	OR = 0.11 [95% CI 0.00-2.32], p = 0.190
ST103CV	OR = 1.00 [95% CI 0.99-1.00], p = 0.198
ST31TA	OR = 9.64 [95% CI 0.31-564.22], p = 0.223
ST57TA	OR = 9.80 [95% CI 0.29-679.80], p = 0.231
ST116CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.242
ST47SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.246
ST58SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.250
ST74CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.275
ST44CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.285
ST31CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.288
ST111CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.294
ST98SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.297
ST39SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.298
ST111SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.309
ST115TA	OR = 6.72 [95% CI 0.18-377.95], p = 0.318
ST36CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.329
ST52SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.341
ST55TA	OR = 10.18 [95% CI 0.09-2034.13], p = 0.348
ST106SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.351
ST111TA	OR = 5.20 [95% CI 0.16-278.21], p = 0.375
ST54CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.384
ST105SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.388
ST58CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.391

FreeSurfer brain areas	Non-significant findings
ST32CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.397
ST52CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.404
ST117CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.407
ST113SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.408
ST95CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.450
ST73TA	OR = 0.37 [95% CI 0.02-4.85], p = 0.454
ST91TA	OR = 3.87 [95% CI 0.11-220.64], p = 0.471
ST45CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.471
ST39TA	OR = 0.20 [95% CI 0.00-15.34], p = 0.471
ST31SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.484
ST115CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.492
ST90TA	OR = 2.92 [95% CI 0.14-81.03], p = 0.498
ST83SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.503
ST47CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.506
ST95SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.507
ST130SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.519
ST36SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.521
ST74TA	OR = 3.00 [95% CI 0.10-110.45], p = 0.531
ST98CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.532
ST15CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.535
ST114SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.539
ST52TA	OR = 3.20 [95% CI 0.08-196.22], p = 0.542
ST40CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.545
ST40TA	OR = 2.69 [95% CI 0.10-94.03], p = 0.557
ST94SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.564
ST83CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.568
ST106CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.579
ST103TA	OR = 0.45 [95% CI 0.02-8.87], p = 0.602
ST56CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.606
ST103SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.610
ST109SA	OR = 1.00 [95% CI 0.99-1.00], p = 0.615
ST32SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.620
ST109CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.624
ST57SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.630
ST14SA	OR = 1.00 [95% CI 1.00-1.01], p = 0.633
ST36TA	OR = 2.87 [95% CI 0.04-334.28], p = 0.636
ST106TA	OR = 3.59 [95% CI 0.01-1196.61], p = 0.649
ST104TA	OR = 3.38 [95% CI 0.02-946.05], p = 0.659
ST94CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.672
ST40SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.678
ST56SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.695
ST91CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.696
ST90CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.705
ST24TA	OR = 0.74 [95% CI 0.14-3.67], p = 0.714
ST83TA	OR = 0.76 [95% CI 0.16-3.44], p = 0.717

FreeSurfer brain areas	Non-significant findings
ST50TA	OR = 0.40 [95% CI 0.00-61.27], p = 0.719
ST129SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.722
ST17SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.736
ST97TA	OR = 0.49 [95% CI 0.01-34.12], p = 0.738
ST116SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.744
ST58TA	OR = 1.78 [95% CI 0.05-67.87], p = 0.748
ST130TA	OR = 0.63 [95% CI 0.02-15.08], p = 0.770
ST98TA	OR = 0.55 [95% CI 0.01-36.03], p = 0.773
ST35TA	OR = 2.00 [95% CI 0.02-282.31], p = 0.777
ST50CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.782
ST39CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.786
ST129CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.788
ST24SA	OR = 1.00 [95% CI 0.99-1.01], p = 0.789
ST46TA	OR = 0.60 [95% CI 0.01-30.03], p = 0.793
ST99TA	OR = 1.50 [95% CI 0.06-44.02], p = 0.806
ST99CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.812
ST130CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.815
ST97CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.818
ST44TA	OR = 1.29 [95% CI 0.13-13.24], p = 0.825
ST38TA	OR = 1.65 [95% CI 0.02-174.89], p = 0.825
ST77SV	OR = 1.00 [95% CI 1.00-1.00], p = 0.828
ST115SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.829
ST114CV	OR = 1.00 [95% CI 1.00-1.00], p = 0.840
ST91SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.844
ST114TA	OR = 1.55 [95% CI 0.02-170.88], p = 0.848
ST109TA	OR = 1.43 [95% CI 0.02-119.03], p = 0.871
ST55SA	OR = 1.00 [95% CI 1.00-1.00], p = 0.896

Appendix D

Supplementary tables of chapter 6 (Study 3)

Table D1

Average Sum of Absolute Differences (SAD) and Mean Absolute Error (MAE)

Method	AVG_SAD	AVG_MAE	AVG_SAD_NORM	AVG_MAE_NORM
MissForest	1024.908	4.362729	31.34886	0.133429
Iterative	1098.951	4.677845	35.36023	0.150499
MICEForest	1368.274	5.82418	44.63414	0.189969

Notes. Metrics are shown for both raw and normalised data. Lower values indicate better imputation accuracy.

Table D2

Proportion of missingness for each neuropsychological features included in the analyses

Variable	Missing %
TRABSCOR	6.26
AVDELTOT	2.25
TRAASCOR	2.22
AVTOTB	1.85
CLOCKSCOR	1.35
COPYSCOR	1.21
CATANIMSC	1.18
TOTAL13	1.15
Q13SCORE	0.59
Q9SCORE	0.34
MMSCORE	0.31
Q8SCORE	0.22
Q1SCORE	0.2
Q4SCORE	0.2
Q5SCORE	0.2
Q6SCORE	0.11
Q7SCORE	0.11
Q10SCORE	0.11
Q11SCORE	0.11
Q12SCORE	0.11
Q2SCORE	0.08
Q3SCORE	0.08

Table D3

Predictors as coded on ADNI and corresponding items

CODE	ITEM
age_at_npi_assessment	Age
PTGENDER	Gender
PTEDUCAT	Education
NPICTOT	Agitation
NPIDTOT	Depression
NPIETOT	Anxiety
NPIFTOT	Elation
NPIGTOT	Apathy
NPIHTOT	Disinhibition
NPIITOT	Irritability
NPIJTOT	Aberrant Motor Behaviour
NPIKTOT	Sleep Disorders
NPILTOT	Appetite Disorders
Q1SCORE	Word Recall
Q2SCORE	Commands
Q3SCORE	Constructional Praxis
Q4SCORE	Delayed Word Recall
Q5SCORE	Naming Objects and Fingers
Q6SCORE	Ideational Praxis
Q7SCORE	Orientation
Q8SCORE	Word Recognition
Q9SCORE	Remembering Test Instructions
Q10SCORE	Comprehension of Spoken Language
Q11SCORE	Word-finding Difficulty
Q12SCORE	Language
Q13SCORE	Number Cancellation
CLOCKSCOR	Clock drawing
COPYSCOR	Clock copying
TRAASCOR	Trail Making Test – Part A
TRABSCOR	Trail Making Test – Part B
AVTOTB	Rey Auditory Verbal Learning Test
AVDELTOT	Rey Auditory Verbal Learning Test - Delayed
CATANIMSC	Category Fluency (Animals)

Notes. In order: demographic variables, the Neuropsychiatric Inventory, the ADAS-Cog-13, and neuropsychological battery. Age was calculated from the ADNI table deriving from the date of birth and the exam date at NPI assessment and recoded into the new column shown here age_at_npi_assessment.

Table D4

Associations of demographic variables between groups of participants with and without psychotic symptoms (divided per group)

Variable	Test	Statistic	df	*p*	Effect Size
		Psychosis			
Age	t	0.16	225.6	.874	0.02
Education	t	-0.27	225.97	.791	-0.04
MMSE	t	-2.61	223.69	**.01**	-0.35
Gender	Chi-square	0	1	1	0
Disease Stage	Chi-square	0	1	1	0
		Delusions			
Age	t	0.11	175.73	.916	0.02
Education	t	-0.18	175.83	.857	-0.03
MMSE	t	-2.78	175.07	**.006**	-0.42
Gender	Chi-square	0	1	1	0
Disease Stage	Chi-square	0	1	1	0
		Hallucinations			
Age	t	0.04	97.99	.969	0.01
Education	t	-0.16	98	.872	-0.03
MMSE	t	-1.83	96.81	**.007**	-0.37
Gender	Chi-square	0	1	1	0
Disease Stage	Fisher exact			1	
		Misidentification			
Age	t	0.01	88	.99	0
Education	t	-0.17	87.91	.868	-0.04
MMSE	t	-2.25	82.18	**.027**	-0.47
Gender	Chi-square	0	1	1	0
Disease Stage	Fisher exact			1	
		Paranoia			
Age	t	0	49.73	1	0
Education	t	-0.12	49.96	.903	-0.03
MMSE	t	0.03	50	.976	0.01
Gender	Chi-square	0	1	1	0
Disease Stage	Fisher exact			1	
		Delusion of Theft			
Age	t	0.03	81.65	.978	0.01
Education	t	-0.13	81.94	.898	-0.03
MMSE	t	-0.34	79.12	.732	-0.08
Gender	Chi-square	0	1	1	0
Disease Stage	Fisher exact			1	

Notes. In bold, significant *p* values.

Table D5

Complete results of univariable analyses of CFA logistic regression models

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
					Psychosis					
Language	1.371	1.042	1.834	**.0281**	1.035	0.619	1.737	.8956	.0562	.0375
Episodic memory	1.414	0.951	2.133	.0912	0.905	0.498	1.651	.7438	.0912	.0912
Visuospatial function	1.532	1.174	2.025	**.0021**	1.564	0.966	2.576	.0724	**.0063**	**.0042**
Attention/ Executive function	1.691	1.24	2.335	**.0011**	1.754	1.046	2.994	**.0354**	**.0044**	**.0042**
					Delusions					
Language	1.195	0.876	1.647	.2645	0.64	0.343	1.16	.148	.2645	.2645
Episodic memory	1.644	1.024	2.709	**.044**	1.237	0.623	2.518	.5479	.176	.1193
Visuospatial function	1.309	0.962	1.797	.0895	0.898	0.498	1.605	.7154	.2625	.1193
Attention/ Executive function	1.371	0.957	1.98	.0875	0.949	0.511	1.75	.8671	.2625	.1193
					Hallucinations					
Language	1.433	0.947	2.254	.0984	2.042	0.849	5.186	.1192	.1968	.1312
Episodic memory	1.126	0.618	2.09	.7002	0.737	0.289	1.862	.5151	.7002	.7002
Visuospatial function	1.643	1.093	2.534	**.0196**	3.618	1.521	9.504	**.0055**	.0588	**.0392**
Attention/ Executive function	1.932	1.179	3.275	**.0109**	3.44	1.495	8.495	**.005**	**.0436**	**.0392**
					Misidentification					
Language	2.128	1.257	3.967	**.0092**	2.644	0.969	7.799	.0651	**.0184**	**.0123**
Episodic memory	2.283	1.198	4.615	**.0155**	2.085	0.624	7.347	.2389	**.0184**	**.0155**
Visuospatial function	1.967	1.247	3.259	**.0054**	2.334	1.012	5.741	.0531	**.0162**	**.0108**
Attention/ Executive function	2.49	1.442	4.558	**.0017**	3.153	1.311	8.172	**.0131**	**.0068**	**.0068**
					Paranoia					
Language	0.744	0.345	1.546	.4321	0.377	0.075	1.461	.1866	1	.568

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Episodic memory	1.291	0.538	3.183	.568	2.448	0.491	13.727	.2844	1	.568
Visuospatial function	0.751	0.388	1.405	.3755	0.4	0.105	1.257	.1401	1	.568
Attention/ Executive function	0.796	0.41	1.505	.4861	0.54	0.167	1.561	.2699	1	.568
Delusion of theft										
Language	0.601	0.246	1.329	.2263	0.434	0.08	1.923	.2912	.9052	.5085
Episodic memory	0.857	0.265	2.668	.7877	1.542	0.271	9.168	.6218	.9858	.7877
Visuospatial function	0.724	0.338	1.475	.3814	0.748	0.171	3.01	.6812	.9858	.5085
Attention/ Executive function	0.679	0.301	1.458	.3286	0.663	0.157	2.534	.5503	.9858	.5085

Notes. In bold, the significant *p* values. *Abbreviations.* OR = odds ratio; CI = confidence interval (95%); M adj = model which included MMSE as covariate; FWE = *p* family wise error corrected (Bonferroni-Holm); FDR = *p* false discovery rate corrected.

Table D6

Multivariable results of the CFA logistic regression models

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Psychosis										
Language	0.562	0.253	1.225	.1498	0.503	.217	1.148	.105	.5992	.502
Episodic memory	0.834	0.464	1.501	.5439	0.733	.375	1.427	.3596	.8565	.5439
Visuospatial function	1.913	0.586	6.414	.2855	1.787	.541	6.048	.3434	.8565	.502
Attention/ Executive function	1.588	0.57	4.464	.3765	1.618	.579	4.561	.3584	.8565	.502
Delusions										
Language	0.434	0.159	1.147	.096	0.357	.125	0.984	.0493	.384	.1612
Episodic memory	1.74	0.875	3.582	.1209	1.346	.623	2.98	.4532	.384	.1612
Visuospatial function	3.278	0.765	14.932	.1148	2.694	.608	12.539	.196	.384	.1612
Attention/ Executive function	0.631	0.188	2.058	.4478	0.662	.195	2.194	.5016	.4478	.4478
Hallucinations										
Language	0.979	0.289	3.251	.9723	0.979	.289	3.251	.9723	1	.9723
Episodic memory	0.433	0.138	1.284	.1367	0.433	.138	1.284	.1367	.5468	.2896
Visuospatial function	1.453	0.241	9.427	.6858	1.453	.241	9.427	.6858	1	.9144
Attention/ Executive function	3.365	0.665	17.893	.1448	3.365	.665	17.893	.1448	.5468	.2896
Misidentification										
Language	2.177	0.516	10.229	.3008	2.842	.611	14.979	.1942	.8826	.4011
Episodic memory	0.729	0.229	2.284	.5857	1.135	.266	4.923	.8633	.8826	.5857
Visuospatial function	0.345	0.044	2.441	.2942	0.41	.05	3.076	.389	.8826	.4011
Attention/ Executive function	5.056	0.902	31.285	.0705	4.46	.771	28.213	.1002	.282	.282

Abbreviations. OR = odds ratio; CI = confidence interval (95%); M adj = model which included MMSE as covariate; FWE = *p* family wise error corrected (Bonferroni-Holm); FDR = *p* false discovery rate corrected.

Table D7

Correlation matrix psychotic cluster

	Q1SCORE	Q2SCORE	Q3SCORE	Q4SCORE	Q5SCORE	Q6SCORE	Q7SCORE	Q8SCORE	Q9SCORE	Q10SCORE	Q11SCORE	Q12SCORE	Q13SCORE	CLOCKSCOR	COPYSCOR	AVTOTB	CATANIMSC	TRAASCOR	TRABSCOR	AVDELTOT
Q1SCORE	1	0.52	0.44	0.67	0.53	0.49	0.63	0.63	0.52	0.51	0.61	0.5	0.56	0.65	0.57	0.58	0.69	0.48	0.56	0.54
Q2SCORE	0.52	1	0.63	0.22	0.65	0.66	0.51	0.36	0.57	0.62	0.63	0.62	0.58	0.6	0.61	0.4	0.57	0.46	0.39	0.26
Q3SCORE	0.44	0.63	1	0.23	0.5	0.65	0.49	0.27	0.48	0.49	0.48	0.47	0.55	0.59	0.64	0.29	0.45	0.46	0.38	0.21
Q4SCORE	0.67	0.22	0.23	1	0.29	0.25	0.57	0.59	0.34	0.26	0.36	0.27	0.33	0.41	0.33	0.35	0.54	0.33	0.4	0.54
Q5SCORE	0.53	0.65	0.5	0.29	1	0.49	0.5	0.43	0.49	0.57	0.59	0.51	0.44	0.56	0.5	0.38	0.58	0.31	0.36	0.31
Q6SCORE	0.49	0.66	0.65	0.25	0.49	1	0.5	0.29	0.53	0.61	0.53	0.6	0.57	0.58	0.68	0.37	0.55	0.5	0.42	0.29
Q7SCORE	0.63	0.51	0.49	0.57	0.5	0.5	1	0.62	0.54	0.48	0.5	0.45	0.57	0.59	0.61	0.4	0.51	0.5	0.48	0.58
Q8SCORE	0.63	0.36	0.27	0.59	0.43	0.29	0.62	1	0.52	0.4	0.41	0.32	0.46	0.47	0.32	0.43	0.53	0.31	0.44	0.49
Q9SCORE	0.52	0.57	0.48	0.34	0.49	0.53	0.54	0.52	1	0.66	0.63	0.65	0.55	0.59	0.49	0.45	0.52	0.43	0.4	0.32
Q10SCORE	0.51	0.62	0.49	0.26	0.57	0.61	0.48	0.4	0.66	1	0.64	0.7	0.51	0.55	0.51	0.45	0.57	0.36	0.39	0.29
Q11SCORE	0.61	0.63	0.48	0.36	0.59	0.53	0.5	0.41	0.63	0.64	1	0.7	0.51	0.57	0.52	0.53	0.6	0.36	0.45	0.32
Q12SCORE	0.5	0.62	0.47	0.27	0.51	0.6	0.45	0.32	0.65	0.7	0.7	1	0.5	0.54	0.53	0.43	0.53	0.34	0.35	0.26
Q13SCORE	0.56	0.58	0.55	0.33	0.44	0.57	0.57	0.46	0.55	0.51	0.51	0.5	1	0.63	0.68	0.47	0.59	0.64	0.6	0.4
CLOCKSCOR	0.65	0.6	0.59	0.41	0.56	0.58	0.59	0.47	0.59	0.55	0.57	0.54	0.63	1	0.76	0.43	0.66	0.61	0.58	0.36
COPYSCOR	0.57	0.61	0.64	0.33	0.5	0.68	0.61	0.32	0.49	0.51	0.52	0.53	0.68	0.76	1	0.41	0.6	0.64	0.48	0.33
AVTOTB	0.58	0.4	0.29	0.35	0.38	0.37	0.4	0.43	0.45	0.45	0.53	0.43	0.47	0.43	0.41	1	0.51	0.36	0.43	0.31
CATANIMSC	0.69	0.57	0.45	0.54	0.58	0.55	0.51	0.53	0.52	0.57	0.6	0.53	0.59	0.66	0.6	0.51	1	0.5	0.57	0.37
TRAASCOR	0.48	0.46	0.46	0.33	0.31	0.5	0.5	0.31	0.43	0.36	0.36	0.34	0.64	0.61	0.64	0.36	0.5	1	0.58	0.29
TRABSCOR	0.56	0.39	0.38	0.4	0.36	0.42	0.48	0.44	0.4	0.39	0.45	0.35	0.6	0.58	0.48	0.43	0.57	0.58	1	0.33
AVDELTOT	0.54	0.26	0.21	0.54	0.31	0.29	0.58	0.49	0.32	0.29	0.32	0.26	0.4	0.36	0.33	0.31	0.37	0.29	0.33	1

Table D8

Correlation matrix delusions

	Q1SCORE	Q2SCORE	Q3SCORE	Q4SCORE	Q5SCORE	Q6SCORE	Q7SCORE	Q8SCORE	Q9SCORE	Q10SCORE	Q11SCORE	Q12SCORE	Q13SCORE	CLOCKSCOR	COPYSCOR	AVTOTB	CATANIMSC	TRAASCOR	TRABSCOR	AVDELTOT
Q1SCORE	1	0.53	0.48	0.7	0.56	0.53	0.66	0.59	0.49	0.55	0.64	0.53	0.55	0.68	0.6	0.56	0.69	0.47	0.59	0.54
Q2SCORE	0.53	1	0.65	0.25	0.67	0.72	0.54	0.34	0.56	0.66	0.64	0.66	0.6	0.68	0.66	0.39	0.61	0.49	0.42	0.3
Q3SCORE	0.48	0.65	1	0.26	0.53	0.71	0.49	0.29	0.49	0.58	0.53	0.52	0.54	0.63	0.64	0.29	0.48	0.43	0.37	0.25
Q4SCORE	0.7	0.25	0.26	1	0.29	0.25	0.55	0.54	0.32	0.28	0.38	0.28	0.33	0.37	0.32	0.31	0.52	0.29	0.4	0.53
Q5SCORE	0.56	0.67	0.53	0.29	1	0.51	0.55	0.41	0.53	0.62	0.6	0.54	0.47	0.6	0.53	0.39	0.58	0.31	0.38	0.35
Q6SCORE	0.53	0.72	0.71	0.25	0.51	1	0.53	0.26	0.51	0.63	0.55	0.63	0.63	0.66	0.73	0.38	0.58	0.55	0.44	0.3
Q7SCORE	0.66	0.54	0.49	0.55	0.55	0.53	1	0.57	0.55	0.57	0.53	0.5	0.61	0.63	0.63	0.39	0.52	0.49	0.52	0.6
Q8SCORE	0.59	0.34	0.29	0.54	0.41	0.26	0.57	1	0.5	0.41	0.38	0.32	0.44	0.46	0.29	0.37	0.5	0.26	0.46	0.46
Q9SCORE	0.49	0.56	0.49	0.32	0.53	0.51	0.55	0.5	1	0.67	0.63	0.66	0.54	0.62	0.49	0.39	0.51	0.42	0.42	0.33
Q10SCORE	0.55	0.66	0.58	0.28	0.62	0.63	0.57	0.41	0.67	1	0.64	0.72	0.56	0.63	0.57	0.42	0.58	0.4	0.4	0.36
Q11SCORE	0.64	0.64	0.53	0.38	0.6	0.55	0.53	0.38	0.63	0.64	1	0.69	0.54	0.64	0.57	0.54	0.61	0.39	0.5	0.36
Q12SCORE	0.53	0.66	0.52	0.28	0.54	0.63	0.5	0.32	0.66	0.72	0.69	1	0.53	0.6	0.54	0.42	0.55	0.37	0.37	0.29
Q13SCORE	0.55	0.6	0.54	0.33	0.47	0.63	0.61	0.44	0.54	0.56	0.54	0.53	1	0.69	0.69	0.44	0.62	0.62	0.63	0.42
CLOCKSCOR	0.68	0.68	0.63	0.37	0.6	0.66	0.63	0.46	0.62	0.63	0.64	0.6	0.69	1	0.76	0.44	0.68	0.6	0.59	0.35
COPYSCOR	0.6	0.66	0.64	0.32	0.53	0.73	0.63	0.29	0.49	0.57	0.57	0.54	0.69	0.76	1	0.38	0.6	0.62	0.47	0.36
AVTOTB	0.56	0.39	0.29	0.31	0.39	0.38	0.39	0.37	0.39	0.42	0.54	0.42	0.44	0.44	0.38	1	0.52	0.35	0.44	0.3
CATANIMSC	0.69	0.61	0.48	0.52	0.58	0.58	0.52	0.5	0.51	0.58	0.61	0.55	0.62	0.68	0.6	0.52	1	0.49	0.59	0.37
TRAASCOR	0.47	0.49	0.43	0.29	0.31	0.55	0.49	0.26	0.42	0.4	0.39	0.37	0.62	0.6	0.62	0.35	0.49	1	0.59	0.28
TRABSCOR	0.59	0.42	0.37	0.4	0.38	0.44	0.52	0.46	0.42	0.4	0.5	0.37	0.63	0.59	0.47	0.44	0.59	0.59	1	0.34
AVDELTOT	0.54	0.3	0.25	0.53	0.35	0.3	0.6	0.46	0.33	0.36	0.36	0.29	0.42	0.35	0.36	0.3	0.37	0.28	0.34	1

Table D9

Correlation matrix hallucinations

	Q1SCORE	Q2SCORE	Q3SCORE	Q4SCORE	Q5SCORE	Q6SCORE	Q7SCORE	Q8SCORE	Q9SCORE	Q10SCORE	Q11SCORE	Q12SCORE	Q13SCORE	CLOCKSCOR	COPYSCOR	AVTOTB	CATANMSC	TRAASCOR	TRABSCOR	AVDELTOT
Q1SCORE	1	0.51	0.48	0.77	0.51	0.48	0.7	0.66	0.58	0.5	0.54	0.51	0.59	0.69	0.58	0.55	0.67	0.51	0.5	0.6
Q2SCORE	0.51	1	0.67	0.22	0.64	0.67	0.53	0.41	0.63	0.68	0.56	0.63	0.61	0.56	0.64	0.37	0.55	0.41	0.33	0.28
Q3SCORE	0.48	0.67	1	0.28	0.51	0.65	0.54	0.33	0.63	0.59	0.52	0.5	0.62	0.62	0.67	0.31	0.49	0.43	0.39	0.26
Q4SCORE	0.77	0.22	0.28	1	0.31	0.28	0.59	0.59	0.36	0.25	0.33	0.26	0.38	0.52	0.4	0.32	0.55	0.41	0.38	0.6
Q5SCORE	0.51	0.64	0.51	0.31	1	0.44	0.51	0.47	0.53	0.65	0.58	0.49	0.4	0.51	0.47	0.38	0.57	0.24	0.29	0.27
Q6SCORE	0.48	0.67	0.65	0.28	0.44	1	0.5	0.32	0.59	0.64	0.47	0.62	0.53	0.51	0.64	0.37	0.53	0.39	0.36	0.32
Q7SCORE	0.7	0.53	0.54	0.59	0.51	0.5	1	0.72	0.56	0.49	0.42	0.43	0.63	0.62	0.66	0.47	0.54	0.5	0.41	0.63
Q8SCORE	0.66	0.41	0.33	0.59	0.47	0.32	0.72	1	0.58	0.43	0.36	0.32	0.55	0.51	0.39	0.46	0.49	0.37	0.36	0.54
Q9SCORE	0.58	0.63	0.63	0.36	0.53	0.59	0.56	0.58	1	0.68	0.64	0.6	0.63	0.56	0.58	0.5	0.57	0.37	0.36	0.37
Q10SCORE	0.5	0.68	0.59	0.25	0.65	0.64	0.49	0.43	0.68	1	0.67	0.7	0.45	0.48	0.51	0.5	0.58	0.17	0.34	0.22
Q11SCORE	0.54	0.56	0.52	0.33	0.58	0.47	0.42	0.36	0.64	0.67	1	0.71	0.46	0.49	0.49	0.48	0.6	0.21	0.31	0.26
Q12SCORE	0.51	0.63	0.5	0.26	0.49	0.62	0.43	0.32	0.6	0.7	0.71	1	0.49	0.5	0.57	0.44	0.55	0.19	0.28	0.3
Q13SCORE	0.59	0.61	0.62	0.38	0.4	0.53	0.63	0.55	0.63	0.45	0.46	0.49	1	0.63	0.72	0.53	0.57	0.64	0.57	0.37
CLOCKSCOR	0.69	0.56	0.62	0.52	0.51	0.51	0.62	0.51	0.56	0.48	0.49	0.5	0.63	1	0.76	0.41	0.66	0.59	0.51	0.43
COPYSCOR	0.58	0.64	0.67	0.4	0.47	0.64	0.66	0.39	0.58	0.51	0.49	0.57	0.72	0.76	1	0.41	0.65	0.63	0.44	0.44
AVTOTB	0.55	0.37	0.31	0.32	0.38	0.37	0.47	0.46	0.5	0.5	0.48	0.44	0.53	0.41	0.41	1	0.5	0.35	0.43	0.34
CATANMSC	0.67	0.55	0.49	0.55	0.57	0.53	0.54	0.49	0.57	0.58	0.6	0.55	0.57	0.66	0.65	0.5	1	0.44	0.49	0.31
TRAASCOR	0.51	0.41	0.43	0.41	0.24	0.39	0.5	0.37	0.37	0.17	0.21	0.19	0.64	0.59	0.63	0.35	0.44	1	0.57	0.27
TRABSCOR	0.5	0.33	0.39	0.38	0.29	0.36	0.41	0.36	0.36	0.34	0.31	0.28	0.57	0.51	0.44	0.43	0.49	0.57	1	0.27
AVDELTOT	0.6	0.28	0.26	0.6	0.27	0.32	0.63	0.54	0.37	0.22	0.26	0.3	0.37	0.43	0.44	0.34	0.31	0.27	0.27	1

Table D10

Correlation matrix misidentification

	Q1SCORE	Q2SCORE	Q3SCORE	Q4SCORE	Q5SCORE	Q6SCORE	Q7SCORE	Q8SCORE	Q9SCORE	Q10SCORE	Q11SCORE	Q12SCORE	Q13SCORE	CLOCKSCOR	COPYSCOR	AVTOTB	CATANIMSC	TRAASCOR	TRABSCOR	AVDELTOT
Q1SCORE	1	0.51	0.43	0.71	0.47	0.44	0.62	0.58	0.49	0.45	0.58	0.48	0.55	0.64	0.58	0.52	0.66	0.49	0.48	0.56
Q2SCORE	0.51	1	0.56	0.2	0.67	0.49	0.39	0.34	0.54	0.62	0.62	0.63	0.56	0.54	0.52	0.37	0.53	0.4	0.3	0.18
Q3SCORE	0.43	0.56	1	0.29	0.47	0.56	0.52	0.26	0.49	0.49	0.42	0.42	0.59	0.62	0.67	0.2	0.46	0.55	0.42	0.23
Q4SCORE	0.71	0.2	0.29	1	0.22	0.28	0.62	0.57	0.36	0.25	0.33	0.28	0.34	0.49	0.39	0.28	0.5	0.41	0.34	0.57
Q5SCORE	0.47	0.67	0.47	0.22	1	0.4	0.4	0.33	0.35	0.56	0.52	0.53	0.38	0.53	0.47	0.35	0.54	0.24	0.26	0.15
Q6SCORE	0.44	0.49	0.56	0.28	0.4	1	0.46	0.21	0.52	0.64	0.46	0.53	0.45	0.49	0.62	0.27	0.53	0.45	0.34	0.26
Q7SCORE	0.62	0.39	0.52	0.62	0.4	0.46	1	0.68	0.48	0.41	0.44	0.37	0.51	0.56	0.54	0.44	0.47	0.49	0.41	0.6
Q8SCORE	0.58	0.34	0.26	0.57	0.33	0.21	0.68	1	0.5	0.38	0.43	0.28	0.46	0.4	0.3	0.43	0.45	0.29	0.34	0.53
Q9SCORE	0.49	0.54	0.49	0.36	0.35	0.52	0.48	0.5	1	0.68	0.58	0.63	0.56	0.51	0.45	0.44	0.59	0.43	0.37	0.3
Q10SCORE	0.45	0.62	0.49	0.25	0.56	0.64	0.41	0.38	0.68	1	0.69	0.74	0.47	0.48	0.46	0.45	0.58	0.28	0.36	0.2
Q11SCORE	0.58	0.62	0.42	0.33	0.52	0.46	0.44	0.43	0.58	0.69	1	0.77	0.53	0.51	0.49	0.42	0.62	0.32	0.34	0.25
Q12SCORE	0.48	0.63	0.42	0.28	0.53	0.53	0.37	0.28	0.63	0.74	0.77	1	0.47	0.5	0.52	0.35	0.57	0.23	0.27	0.2
Q13SCORE	0.55	0.56	0.59	0.34	0.38	0.45	0.51	0.46	0.56	0.47	0.53	0.47	1	0.58	0.64	0.56	0.55	0.65	0.56	0.37
CLOCKSCOR	0.64	0.54	0.62	0.49	0.53	0.49	0.56	0.4	0.51	0.48	0.51	0.5	0.58	1	0.77	0.39	0.68	0.68	0.54	0.37
COPYSCOR	0.58	0.52	0.67	0.39	0.47	0.62	0.54	0.3	0.45	0.46	0.49	0.52	0.64	0.77	1	0.4	0.65	0.59	0.44	0.34
AVTOTB	0.52	0.37	0.2	0.28	0.35	0.27	0.44	0.43	0.44	0.45	0.42	0.35	0.56	0.39	0.4	1	0.45	0.37	0.48	0.34
CATANIMSC	0.66	0.53	0.46	0.5	0.54	0.53	0.47	0.45	0.59	0.58	0.62	0.57	0.55	0.68	0.65	0.45	1	0.51	0.42	0.28
TRAASCOR	0.49	0.4	0.55	0.41	0.24	0.45	0.49	0.29	0.43	0.28	0.32	0.23	0.65	0.68	0.59	0.37	0.51	1	0.58	0.29
TRABSCOR	0.48	0.3	0.42	0.34	0.26	0.34	0.41	0.34	0.37	0.36	0.34	0.27	0.56	0.54	0.44	0.48	0.42	0.58	1	0.29
AVDELTOT	0.56	0.18	0.23	0.57	0.15	0.26	0.6	0.53	0.3	0.2	0.25	0.2	0.37	0.37	0.34	0.34	0.28	0.29	0.29	1

Table D11

Correlation matrix paranoia

	Q1SCORE	Q2SCORE	Q3SCORE	Q4SCORE	Q5SCORE	Q6SCORE	Q7SCORE	Q8SCORE	Q9SCORE	Q10SCORE	Q11SCORE	Q12SCORE	Q13SCORE	CLOCKSCOR	COPYSCOR	AVTOTB	CATANIMSC	TRAASCOR	TRABSCOR	AVDELTOT
Q1SCORE	1	0.45	0.36	0.74	0.43	0.49	0.62	0.46	0.35	0.49	0.59	0.43	0.39	0.58	0.59	0.6	0.58	0.47	0.55	0.57
Q2SCORE	0.45	1	0.42	0.21	0.45	0.56	0.43	0.24	0.4	0.44	0.59	0.48	0.6	0.66	0.48	0.38	0.48	0.53	0.4	0.33
Q3SCORE	0.36	0.42	1	0.18	0.26	0.65	0.23	0.11	0.19	0.12	0.4	0.21	0.46	0.6	0.56	0.19	0.32	0.45	0.48	0.06
Q4SCORE	0.74	0.21	0.18	1	0.29	0.23	0.6	0.5	0.33	0.28	0.43	0.27	0.11	0.39	0.27	0.36	0.46	0.28	0.4	0.52
Q5SCORE	0.43	0.45	0.26	0.29	1	0.15	0.49	0.32	0.24	0.11	0.28	0.27	0.28	0.45	0.29	0.37	0.47	0.38	0.39	0.37
Q6SCORE	0.49	0.56	0.65	0.23	0.15	1	0.31	0.05	0.32	0.35	0.57	0.42	0.56	0.61	0.71	0.31	0.47	0.56	0.42	0.21
Q7SCORE	0.62	0.43	0.23	0.6	0.49	0.31	1	0.39	0.35	0.3	0.46	0.39	0.38	0.55	0.51	0.3	0.42	0.44	0.49	0.62
Q8SCORE	0.46	0.24	0.11	0.5	0.32	0.05	0.39	1	0.44	0.35	0.37	0.27	0.22	0.45	0.12	0.26	0.41	0.21	0.4	0.24
Q9SCORE	0.35	0.4	0.19	0.33	0.24	0.32	0.35	0.44	1	0.54	0.7	0.78	0.34	0.59	0.25	0.38	0.44	0.51	0.38	0.3
Q10SCORE	0.49	0.44	0.12	0.28	0.11	0.35	0.3	0.35	0.54	1	0.5	0.66	0.38	0.46	0.34	0.35	0.46	0.41	0.23	0.21
Q11SCORE	0.59	0.59	0.4	0.43	0.28	0.57	0.46	0.37	0.7	0.5	1	0.72	0.41	0.68	0.44	0.56	0.49	0.47	0.41	0.42
Q12SCORE	0.43	0.48	0.21	0.27	0.27	0.42	0.39	0.27	0.78	0.66	0.72	1	0.37	0.49	0.28	0.47	0.38	0.51	0.28	0.34
Q13SCORE	0.39	0.6	0.46	0.11	0.28	0.56	0.38	0.22	0.34	0.38	0.41	0.37	1	0.56	0.69	0.36	0.41	0.69	0.52	0.3
CLOCKSCOR	0.58	0.66	0.6	0.39	0.45	0.61	0.55	0.45	0.59	0.46	0.68	0.49	0.56	1	0.62	0.35	0.58	0.57	0.58	0.33
COPYSCOR	0.59	0.48	0.56	0.27	0.29	0.71	0.51	0.12	0.25	0.34	0.44	0.28	0.69	0.62	1	0.3	0.44	0.69	0.5	0.31
AVTOTB	0.6	0.38	0.19	0.36	0.37	0.31	0.3	0.26	0.38	0.35	0.56	0.47	0.36	0.35	0.3	1	0.42	0.37	0.37	0.42
CATANIMSC	0.58	0.48	0.32	0.46	0.47	0.47	0.42	0.41	0.44	0.46	0.49	0.38	0.41	0.58	0.44	0.42	1	0.49	0.56	0.37
TRAASCOR	0.47	0.53	0.45	0.28	0.38	0.56	0.44	0.21	0.51	0.41	0.47	0.51	0.69	0.57	0.69	0.37	0.49	1	0.58	0.33
TRABSCOR	0.55	0.4	0.48	0.4	0.39	0.42	0.49	0.4	0.38	0.23	0.41	0.28	0.52	0.58	0.5	0.37	0.56	0.58	1	0.22
AVDELTOT	0.57	0.33	0.06	0.52	0.37	0.21	0.62	0.24	0.3	0.21	0.42	0.34	0.3	0.33	0.31	0.42	0.37	0.33	0.22	1

Table D12

Correlation matrix delusion of theft

	Q1SCORE	Q2SCORE	Q3SCORE	Q4SCORE	Q5SCORE	Q6SCORE	Q7SCORE	Q8SCORE	Q9SCORE	Q10SCORE	Q11SCORE	Q12SCORE	Q13SCORE	CLOCKSCOR	COPYSCOR	AVTOTB	CATANIMSC	TRAASCOR	TRABSCOR	AVDELTOT
Q1SCORE	1	0.41	0.41	0.67	0.34	0.43	0.6	0.33	0.29	0.44	0.6	0.48	0.39	0.57	0.58	0.73	0.54	0.54	0.61	0.58
Q2SCORE	0.41	1	0.45	0.12	0.57	0.61	0.52	0.19	0.41	0.49	0.58	0.64	0.63	0.66	0.46	0.46	0.5	0.71	0.45	0.44
Q3SCORE	0.41	0.45	1	0.17	0.36	0.68	0.28	0.14	0.14	0.31	0.33	0.34	0.48	0.61	0.61	0.26	0.42	0.53	0.45	0.14
Q4SCORE	0.67	0.12	0.17	1	0.22	0.15	0.56	0.46	0.32	0.23	0.42	0.29	0.06	0.37	0.2	0.48	0.51	0.33	0.49	0.49
Q5SCORE	0.34	0.57	0.36	0.22	1	0.21	0.42	0.18	0.09	0.16	0.29	0.27	0.36	0.47	0.23	0.38	0.54	0.41	0.46	0.26
Q6SCORE	0.43	0.61	0.68	0.15	0.21	1	0.34	-0.04	0.32	0.55	0.48	0.65	0.62	0.56	0.66	0.41	0.53	0.54	0.41	0.26
Q7SCORE	0.6	0.52	0.28	0.56	0.42	0.34	1	0.3	0.23	0.39	0.47	0.42	0.39	0.56	0.5	0.42	0.45	0.49	0.45	0.62
Q8SCORE	0.33	0.19	0.14	0.46	0.18	-0.04	0.3	1	0.49	0.31	0.32	0.21	0.2	0.41	0.03	0.28	0.35	0.33	0.38	0.13
Q9SCORE	0.29	0.41	0.14	0.32	0.09	0.32	0.23	0.49	1	0.65	0.69	0.7	0.24	0.55	0.04	0.36	0.41	0.41	0.33	0.22
Q10SCORE	0.44	0.49	0.31	0.23	0.16	0.55	0.39	0.31	0.65	1	0.52	0.82	0.39	0.5	0.31	0.3	0.47	0.45	0.32	0.2
Q11SCORE	0.6	0.58	0.33	0.42	0.29	0.48	0.47	0.32	0.69	0.52	1	0.74	0.36	0.63	0.37	0.66	0.49	0.44	0.41	0.49
Q12SCORE	0.48	0.64	0.34	0.29	0.27	0.65	0.42	0.21	0.7	0.82	0.74	1	0.43	0.54	0.31	0.51	0.5	0.46	0.32	0.35
Q13SCORE	0.39	0.63	0.48	0.06	0.36	0.62	0.39	0.2	0.24	0.39	0.36	0.43	1	0.56	0.65	0.43	0.41	0.75	0.52	0.31
CLOCKSCOR	0.57	0.66	0.61	0.37	0.47	0.56	0.56	0.41	0.55	0.5	0.63	0.54	0.56	1	0.62	0.43	0.65	0.63	0.56	0.4
COPYSCOR	0.58	0.46	0.61	0.2	0.23	0.66	0.5	0.03	0.04	0.31	0.37	0.31	0.65	0.62	1	0.35	0.43	0.61	0.48	0.33
AVTOTB	0.73	0.46	0.26	0.48	0.38	0.41	0.42	0.28	0.36	0.3	0.66	0.51	0.43	0.43	0.35	1	0.52	0.41	0.51	0.46
CATANIMSC	0.54	0.5	0.42	0.51	0.54	0.53	0.45	0.35	0.41	0.47	0.49	0.5	0.41	0.65	0.43	0.52	1	0.49	0.57	0.44
TRAASCOR	0.54	0.71	0.53	0.33	0.41	0.54	0.49	0.33	0.41	0.45	0.44	0.46	0.75	0.63	0.61	0.41	0.49	1	0.66	0.39
TRABSCOR	0.61	0.45	0.45	0.49	0.46	0.41	0.45	0.38	0.33	0.32	0.41	0.32	0.52	0.56	0.48	0.51	0.57	0.66	1	0.27
AVDELTOT	0.58	0.44	0.14	0.49	0.26	0.26	0.62	0.13	0.22	0.2	0.49	0.35	0.31	0.4	0.33	0.46	0.44	0.39	0.27	1

Table D13

Complete results of univariable analyses of individual neuropsychological tests logistic regression models

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Psychosis										
Q1SCORE	1.308	0.983	1.756	.0681	0.986	0.648	1.503	.9459	.5448	.1048
Q2SCORE	1.065	0.889	1.282	.4944	0.808	0.619	1.049	.1121	1	.5204
Q3SCORE	1.11	0.898	1.379	.3374	0.877	0.659	1.163	.362	1	.3749
Q4SCORE	1.339	0.918	1.998	.1376	1.025	0.652	1.633	.9155	.8256	.1819
Q5SCORE	1.115	0.924	1.356	.2617	0.918	0.713	1.18	.5016	1	.3079
Q6SCORE	1.246	1.038	1.514	**.0211**	1.114	0.871	1.434	.3936	.2743	.0505
Q7SCORE	1.391	1.088	1.791	**.0093**	1.218	0.818	1.824	.3329	.1581	**.0369**
Q8SCORE	1.237	0.931	1.653	.1455	0.992	0.697	1.412	.9634	.8256	.1819
Q9SCORE	1.201	1.004	1.447	**.0485**	1.047	0.822	1.337	.7086	.4365	.0808
Q10SCORE	1.29	1.069	1.577	**.0098**	1.178	0.917	1.524	.2044	.1581	**.0369**
Q11SCORE	1.185	0.974	1.45	.0935	0.997	0.763	1.299	.9802	.6545	.1336
Q12SCORE	1.244	1.036	1.515	**.0232**	1.113	0.872	1.43	.3913	.2784	.0505
Q13SCORE	1.359	1.07	1.737	**.0129**	1.179	0.835	1.673	.3503	.186	**.0369**
CLOCKSCOR	1.335	1.067	1.68	**.0124**	1.169	0.842	1.631	.3523	.186	**.0369**
COPYSCOR	1.406	1.152	1.731	**.001**	1.383	1.035	1.869	**.031**	**.02**	**.02**
AVTOTB	1.424	1.044	1.961	**.0275**	1.234	0.871	1.76	.2395	.3025	.0505
CATANIMSC	1.415	1.044	1.942	**.0278**	1.148	0.76	1.751	.5138	.3025	.0505
TRAASCOR	1.434	1.148	1.815	**.002**	1.335	1.021	1.772	**.0387**	**.038**	**.02**
TRABSCOR	1.509	1.136	2.02	**.005**	1.347	0.966	1.89	.0811	.09	**.0333**
AVDELTOT	0.983	0.755	1.279	.898	0.758	0.55	1.037	.0866	1	.898
Delusions										
Q1SCORE	1.544	1.109	2.186	**.0116**	1.402	0.864	2.316	.1765	.2204	.116
Q2SCORE	0.996	0.799	1.237	.9681	0.695	0.499	0.951	**.0262**	1	.9681

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Q3SCORE	1.067	0.836	1.366	.6042	0.815	0.583	1.129	.222	1	.636
Q4SCORE	2.049	1.271	3.519	**.0053**	1.832	1.044	3.42	**.044**	.106	.106
Q5SCORE	1.103	0.889	1.382	.3769	0.882	0.651	1.189	.4087	1	.4711
Q6SCORE	1.117	0.905	1.388	.3071	0.884	0.645	1.197	.4288	1	.4387
Q7SCORE	1.38	1.038	1.852	**.0284**	1.182	0.734	1.916	.4912	.5112	.1536
Q8SCORE	1.173	0.845	1.637	.3429	0.958	0.651	1.407	.8246	1	.4572
Q9SCORE	1.216	0.988	1.512	.0691	1.073	0.814	1.418	.6142	.9675	.1536
Q10SCORE	1.258	1.011	1.593	**.0453**	1.11	0.812	1.529	.5137	.7248	.1536
Q11SCORE	1.177	0.939	1.483	.1592	0.97	0.704	1.329	.8485	1	.2752
Q12SCORE	1.238	0.994	1.571	.0645	1.089	0.809	1.472	.5736	.9675	.1536
Q13SCORE	1.083	0.816	1.44	.5792	0.713	0.46	1.084	.1197	1	.636
CLOCKSCOR	1.213	0.925	1.598	.1651	0.89	0.577	1.364	.5929	1	.2752
COPYSCOR	1.288	1.025	1.634	**.0326**	1.139	0.815	1.604	.4474	.5542	.1536
AVTOTB	1.39	0.966	2.028	.0802	1.206	0.808	1.817	.362	.9675	.1604
CATANIMSC	1.401	0.983	2.034	.0679	1.119	0.691	1.832	.6497	.9675	.1536
TRAASCOR	1.27	0.991	1.651	.0648	1.124	0.834	1.528	.446	.9675	.1536
TRABSCOR	1.219	0.877	1.704	.2403	0.992	0.668	1.472	.9694	1	.3697
AVDELTOT	1.126	0.826	1.541	.4547	0.909	0.627	1.313	.613	1	.5349
					Hallucinations					
Q1SCORE	1.083	0.711	1.665	.7094	0.808	0.424	1.533	.5116	1	.8346
Q2SCORE	1.077	0.818	1.425	.5917	0.925	0.615	1.388	.7052	1	.7396
Q3SCORE	1.121	0.82	1.549	.4742	0.981	0.62	1.549	.9325	1	.6323
Q4SCORE	0.938	0.538	1.65	.8196	0.723	0.367	1.405	.3345	1	.9107
Q5SCORE	1.114	0.849	1.481	.4387	1.023	0.717	1.464	.8992	1	.6267
Q6SCORE	1.281	0.987	1.7	.0704	1.32	0.927	1.928	.1323	1	.2363
Q7SCORE	1.312	0.892	1.956	.1722	1.33	0.695	2.598	.3923	1	.3444
Q8SCORE	0.989	0.63	1.547	.9611	0.746	0.405	1.342	.3331	1	.979

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Q9SCORE	1.19	0.899	1.597	.2295	1.139	0.762	1.719	.5259	1	.4173
Q10SCORE	1.276	0.973	1.713	.0864	1.281	0.905	1.843	.1685	1	.2363
Q11SCORE	1.159	0.856	1.579	.3408	1.075	0.728	1.589	.7147	1	.5243
Q12SCORE	1.227	0.946	1.63	.1337	1.208	0.866	1.712	.2724	1	.2971
Q13SCORE	1.56	1.075	2.308	**.0216**	1.978	1.116	3.661	**.0233**	.3816	.108
CLOCKSCOR	1.359	0.969	1.928	.0787	1.44	0.88	2.411	.152	1	.2363
COPYSCOR	1.423	1.066	1.929	**.019**	1.844	1.139	3.155	**.0175**	.361	.108
AVTOTB	1.521	0.94	2.531	.0945	1.456	0.851	2.57	.1785	1	.2363
CATANIMSC	1.284	0.812	2.086	.2942	1.158	0.63	2.189	.6395	1	.4903
TRAASCOR	1.519	1.074	2.196	**.0212**	1.541	1.032	2.354	**.0381**	.3816	.108
TRABSCOR	1.975	1.187	3.506	**.0127**	1.986	1.136	3.691	**.021**	.254	.108
AVDELTOT	1.006	0.65	1.559	.979	0.827	0.479	1.405	.4862	1	.979
Misidentification										
Q1SCORE	1.402	0.888	2.272	.1549	0.902	0.451	1.797	.7673	.948	.2047
Q2SCORE	1.187	0.868	1.661	.293	0.88	0.562	1.367	.5686	1	.3447
Q3SCORE	1.45	0.992	2.203	.0653	1.166	0.695	1.979	.562	.7073	.1132
Q4SCORE	1.216	0.671	2.278	.522	0.744	0.35	1.57	.4315	1	.522
Q5SCORE	1.476	1.041	2.237	**.043**	1.278	0.822	2.062	.2902	.516	.0956
Q6SCORE	1.575	1.159	2.278	**.0073**	1.485	1.013	2.304	.0552	.1387	**.0415**
Q7SCORE	1.669	1.098	2.616	**.0198**	1.431	0.751	2.785	.279	.3088	.0612
Q8SCORE	1.45	0.9	2.388	.1329	1.068	0.579	1.973	.8326	.948	.1899
Q9SCORE	1.12	0.844	1.503	.4365	0.872	0.594	1.26	.4679	1	.4595
Q10SCORE	1.603	1.157	2.354	**.0083**	1.49	1.008	2.289	.0537	.1411	**.0415**
Q11SCORE	1.409	0.99	2.06	.0643	1.146	0.704	1.867	.5795	.7073	.1132
Q12SCORE	1.275	0.954	1.779	.1185	1.056	0.717	1.583	.7835	.948	.1823
Q13SCORE	2.122	1.396	3.367	**.0007**	2.278	1.286	4.282	**.0068**	**.014**	**.014**
CLOCKSCOR	1.515	1.063	2.202	**.0245**	1.296	0.776	2.204	.3254	.336	.0612

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
COPYSCOR	1.478	1.076	2.083	**.0193**	1.315	0.825	2.145	.2551	.3088	.0612
AVTOTB	1.424	0.873	2.38	.1638	1.159	0.671	2.023	.5959	.948	.2047
CATANIMSC	1.67	0.977	2.967	.0679	1.195	0.572	2.548	.636	.7073	.1132
TRAASCOR	1.553	1.071	2.313	**.024**	1.349	0.859	2.145	.1929	.336	.0612
TRABSCOR	2.02	1.236	3.485	**.0073**	1.778	1.035	3.191	**.0432**	.1387	**.0415**
AVDELTOT	1.248	0.808	1.954	.3214	0.948	0.557	1.597	.841	1	.3571
					Paranoia					
Q1SCORE	1.509	0.804	2.99	.212	2.352	0.945	6.581	.0796	1	.7892
Q2SCORE	0.743	0.444	1.15	.2067	0.607	0.302	1.08	.1139	1	.7892
Q3SCORE	0.524	0.273	0.927	**.0356**	0.415	0.186	0.82	**.0182**	.712	.486
Q4SCORE	2.753	1.112	8.559	**.0486**	4.64	1.476	19.245	**.0179**	.9234	.486
Q5SCORE	1.233	0.723	2.163	.4469	1.324	0.717	2.532	.3754	1	.7892
Q6SCORE	0.734	0.405	1.229	.2604	0.61	0.271	1.181	.1743	1	.7892
Q7SCORE	1.181	0.676	2.096	.5595	1.525	0.637	3.873	.3513	1	.7892
Q8SCORE	1.073	0.591	1.962	.8155	1.093	0.568	2.122	.7891	1	.8584
Q9SCORE	1.169	0.808	1.742	.4151	1.241	0.807	1.974	.3346	1	.7892
Q10SCORE	1.098	0.692	1.773	.6902	1.14	0.666	1.995	.6326	1	.812
Q11SCORE	1.169	0.711	1.962	.5393	1.386	0.684	2.926	.3717	1	.7892
Q12SCORE	1.194	0.718	2.104	.502	1.299	0.705	2.528	.4098	1	.7892
Q13SCORE	0.77	0.453	1.271	.3145	0.649	0.312	1.245	.2112	1	.7892
CLOCKSCOR	0.888	0.514	1.519	.6648	0.771	0.332	1.735	.5315	1	.812
COPYSCOR	0.882	0.549	1.393	.5919	0.79	0.403	1.491	.4713	1	.7892
AVTOTB	1.558	0.754	3.42	.2426	1.734	0.774	4.235	.1959	1	.7892
CATANIMSC	0.912	0.425	1.936	.8083	0.861	0.314	2.319	.7653	1	.8584
TRAASCOR	0.839	0.543	1.235	.3901	0.736	0.396	1.233	.2755	1	.7892
TRABSCOR	1.047	0.58	1.9	.8772	1.075	0.529	2.2	.8406	1	.8772
AVDELTOT	1.229	0.68	2.27	.4962	1.365	0.665	2.891	.4008	1	.7892

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Delusions of theft										
Q1SCORE	1.25	0.558	2.942	.5888	2.449	0.779	8.944	.1416	1	.7351
Q2SCORE	0.664	0.356	1.086	.1359	0.564	0.235	1.165	.1492	1	.7351
Q3SCORE	0.67	0.337	1.25	.2218	0.687	0.305	1.452	.3337	1	.7351
Q4SCORE	1.865	0.646	6.64	.2777	3.244	0.908	15.125	.0926	1	.7351
Q5SCORE	1	0.525	1.904	1	1.16	0.564	2.459	.6872	1	1
Q6SCORE	0.663	0.334	1.139	.1724	0.641	0.275	1.275	.2369	1	.7351
Q7SCORE	0.766	0.381	1.489	.4355	0.859	0.296	2.44	.7728	1	.7351
Q8SCORE	0.856	0.418	1.717	.6616	0.946	0.437	2.033	.8859	1	.7351
Q9SCORE	1.1	0.728	1.697	.6495	1.268	0.787	2.134	.3395	1	.7351
Q10SCORE	0.717	0.356	1.299	.2947	0.745	0.331	1.57	.4473	1	.7351
Q11SCORE	1.189	0.696	2.091	.5284	1.799	0.863	4.124	.1339	1	.7351
Q12SCORE	0.837	0.481	1.37	.4866	0.913	0.471	1.73	.7786	1	.7351
Q13SCORE	0.62	0.326	1.097	.1153	0.567	0.23	1.199	.1632	1	.7351
CLOCKSCOR	0.943	0.501	1.761	.8519	1.508	0.523	4.618	.4513	1	.8967
COPYSCOR	0.833	0.49	1.37	.4764	0.914	0.457	1.805	.7917	1	.7351
AVTOTB	1.578	0.728	3.717	.2623	2.596	0.969	8.868	.0824	1	.7351
CATANIMSC	0.718	0.294	1.664	.444	0.826	0.254	2.634	.744	1	.7351
TRAASCOR	0.709	0.397	1.213	.2198	0.675	0.28	1.468	.3358	1	.7351
TRABSCOR	1.234	0.61	2.586	.5602	1.726	0.731	4.421	.2257	1	.7351
AVDELTOT	0.741	0.359	1.47	.3976	0.811	0.329	1.944	.6373	1	.7351

Notes. In bold, the significant p values. *Abbreviations.* OR = odds ratio; CI = confidence interval (95%); M adj = model which included MMSE as covariate; FWE = *p* family wise error corrected (Bonferroni-Holm); FDR = *p* false discovery rate corrected.

Table D14

Multivariable results of the individual neuropsychological tests logistic regression models

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
					Psychosis					
AVTOTB	1.105	0.752	1.627	.6097	1.097	0.745	1.616	.6385	1	.8617
CATANIMSC	0.907	0.549	1.491	.6997	0.936	0.564	1.552	.7963	1	.8617
CLOCKSCOR	0.84	0.556	1.256	.3987	0.863	0.568	1.299	.4833	1	.8617
COPYSCOR	1.309	0.908	1.899	.1505	1.337	0.924	1.953	.1258	1	.8617
Q12SCORE	1.102	0.856	1.424	.4521	1.146	0.874	1.511	.3254	1	.8617
Q4SCORE	0.997	0.595	1.68	.9905	1.036	0.613	1.763	.8954	1	.9905
Q6SCORE	0.946	0.712	1.252	.6969	0.967	0.724	1.29	.821	1	.8617
Q7SCORE	1.056	0.726	1.534	.7755	1.157	0.746	1.801	.5155	1	.8617
TRAASCOR	1.19	0.862	1.664	.2981	1.206	0.871	1.694	.268	1	.8617
TRABSCOR	1.21	0.813	1.809	.3482	1.199	0.805	1.795	.372	1	.8617
					Delusions					
Q1SCORE	0.98	0.509	1.886	.9507	1.012	0.523	1.967	.9711	1	.9507
Q4SCORE	2.014	0.999	4.239	.0559	2.078	1.023	4.422	**.0486**	.5588	.5588
Q7SCORE	0.938	0.592	1.478	.7815	1.025	0.607	1.733	.9258	1	.9371
Q10SCORE	1.119	0.787	1.602	.5302	1.16	0.804	1.687	.4287	1	.7983
Q12SCORE	1.034	0.74	1.444	.8434	1.062	0.754	1.496	.7278	1	.9371
COPYSCOR	1.124	0.777	1.63	.5344	1.167	0.795	1.726	.4305	1	.7983
TRAASCOR	1.126	0.794	1.62	.5109	1.147	0.804	1.666	.4555	1	.7983
CATANIMSC	0.835	0.454	1.529	.5588	0.869	0.467	1.615	.6544	1	.7983
TRABSCOR	0.85	0.521	1.374	.5081	0.844	0.516	1.367	.4921	1	.7983
AVTOTB	1.159	0.726	1.86	.5356	1.133	0.706	1.826	.6036	1	.7983
					Hallucinations					
Q5SCORE	0.922	0.668	1.271	.6174	1.136	0.772	1.692	.5185	1	.8506

Predictor	OR	CI lower	CI upper	*p* raw	OR M adj	CI lower M adj	CI upper M adj	*p* M adj	*p* FWE	*p* FDR
Q13SCORE	1.059	0.574	1.931	.8506	1.422	0.714	2.901	.3195	1	.8506
COPYSCOR	1.23	0.784	1.946	.3671	1.629	0.949	2.959	.0884	1	.8506
TRAASCOR	1.08	0.647	1.807	.7654	1.045	0.604	1.785	.8733	1	.8506
TRABSCOR	1.597	0.837	3.178	.1645	1.58	0.819	3.172	.1811	.8227	.8227
Misidentification										
COPYSCOR	0.941	0.591	1.482	.7915	1.174	0.694	2.032	.5533	1	.7915
Q10SCORE	1.292	0.881	1.971	.2054	1.482	0.98	2.334	.0721	.8216	.5135
Q13SCORE	1.667	0.928	3.111	.0943	2.082	1.09	4.248	**.0326**	.4715	.4715
Q7SCORE	1.112	0.645	1.914	.7	1.68	0.826	3.558	.1592	1	.7915
TRABSCOR	1.268	0.683	2.409	.4554	1.172	0.622	2.244	.6247	1	.759

Notes. In bold, the significant p values. *Abbreviations.* OR = odds ratio; CI = confidence interval (95%); M adj = model which included MMSE as covariate; FWE = *p* family wise error corrected (Bonferroni-Holm); FDR = *p* false discovery rate corrected.

Appendix E

Supplementary tables and figures of chapter 7 (Study 4)

Figure E1

Logistic Regression output

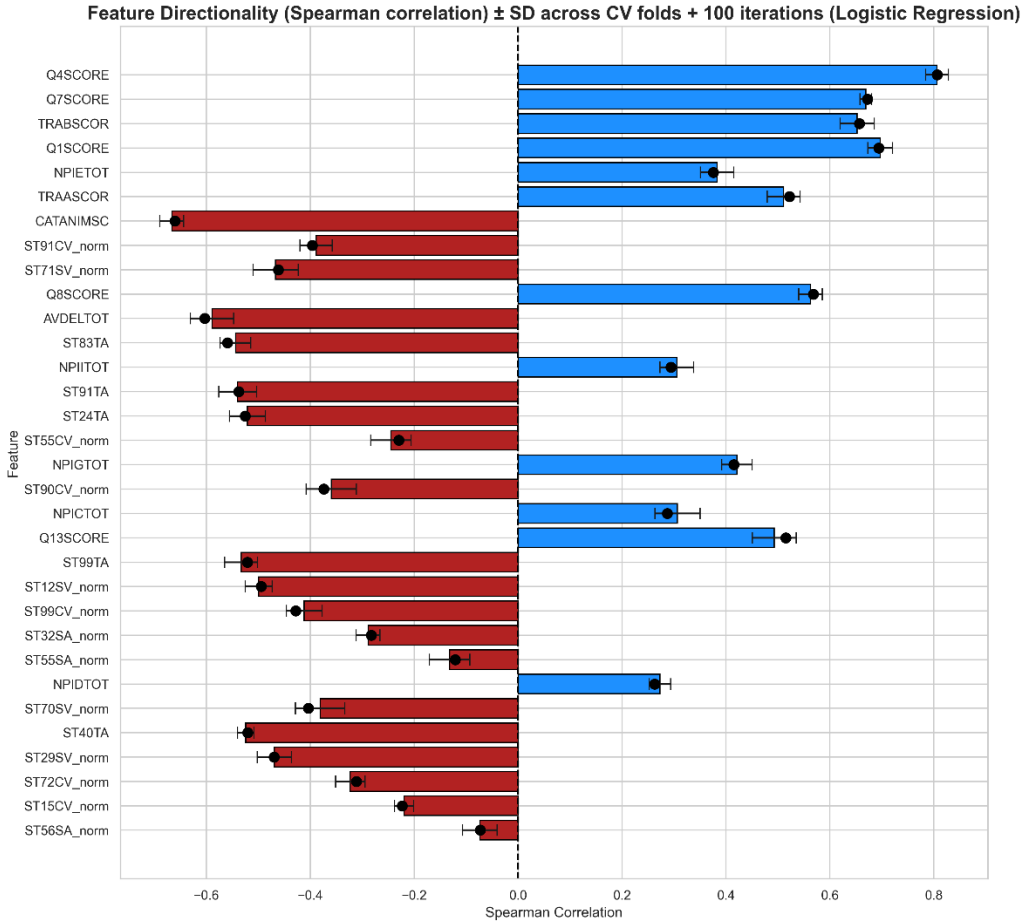


Figure E2

Average confusion matrix based on counts of true and predicted classes across all iterations

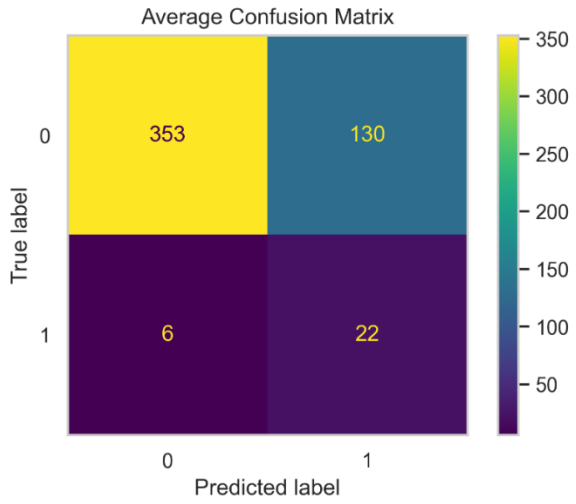
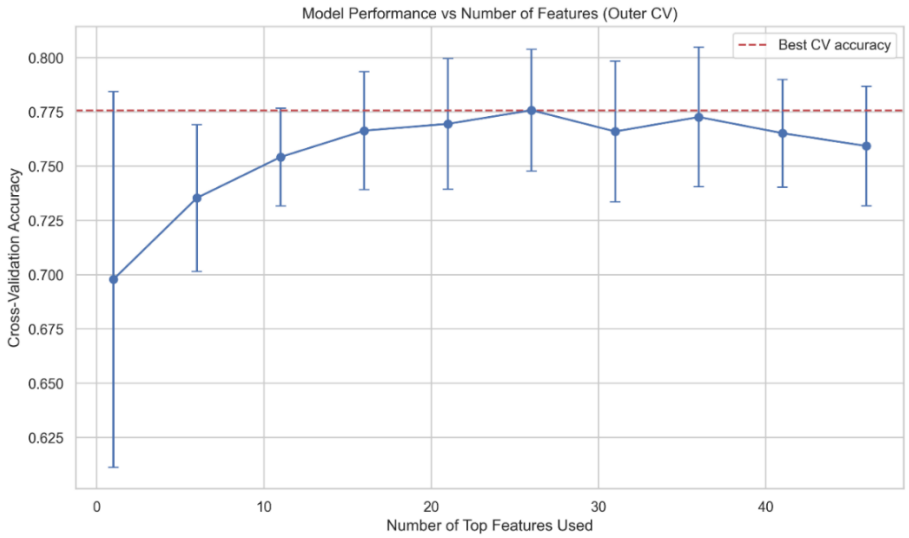


Figure E3

Outer CV model accuracy across cumulative MDI-ranked features



Notes. Outer cross-validation accuracy as a function of the number of MDI-ranked features included. Performance plateaus after ~26 features, suggesting that this subset is sufficient to capture most predictive power.

Table E1

Predictors as coded on ADNI and corresponding items

CODE	ITEM
age_at_npi_assessment	Age
PTGENDER	Gender
PTEDUCAT	Education
NPICTOT	Agitation
NPIDTOT	Depression
NPIETOT	Anxiety
NPIFTOT	Elation
NPIGTOT	Apathy
NPIHTOT	Disinhibition
NPIITOT	Irritability
NPIJTOT	Aberrant Motor Behaviour
NPIKTOT	Sleep Disorders
NPILTOT	Appetite Disorders
Q1SCORE	Word Recall
Q2SCORE	Commands
Q3SCORE	Constructional Praxis
Q4SCORE	Delayed Word Recall
Q5SCORE	Naming Objects and Fingers
Q6SCORE	Ideational Praxis
Q7SCORE	Orientation
Q8SCORE	Word Recognition
Q9SCORE	Remembering Test Instructions
Q10SCORE	Comprehension of Spoken Language
Q11SCORE	Word-finding Difficulty
Q12SCORE	Language
Q13SCORE	Number Cancellation
CLOCKSCOR	Clock drawing
COPYSCOR	Clock copying
TRAASCOR	Trail Making Test – Part A
TRABSCOR	Trail Making Test – Part B
AVTOTB	Rey Auditory Verbal Learning Test
AVDELTOT	Rey Auditory Verbal Learning Test - Delayed
CATANIMSC	Category Fluency (Animals)

Notes. Items in order: demographic variables, the Neuropsychiatric Inventory, the ADAS-Cog-13, and neuropsychological battery Age was calculated from the ADNI table deriving from the date of birth and the exam date at NPI assessment and recoded into the new column shown here age_at_npi_assessment.

Table E2

Brain regions derived from FreeSurfer, as made available on ADNI

CODE	LABEL
ST101SV	Subcortical Volume (aseg.stats) of RightPallidum
ST102CV	Cortical Volume (aparc.stats) of RightParacentral
ST102SA	Surface Area (aparc.stats) of RightParacentral
ST102TA	Thickness Average (aparc.stats) of RightParacentral
ST102TS	Thickness Stardard Deviation (aparc.stats) of RightParacentral
ST103CV	Cortical Volume (aparc.stats) of RightParahippocampal
ST103SA	Surface Area (aparc.stats) of RightParahippocampal
ST103TA	Thickness Average (aparc.stats) of RightParahippocampal
ST103TS	Thickness Stardard Deviation (aparc.stats) of RightParahippocampal
ST104CV	Cortical Volume (aparc.stats) of RightParsOpercularis
ST104SA	Surface Area (aparc.stats) of RightParsOpercularis
ST104TA	Thickness Average (aparc.stats) of RightParsOpercularis
ST104TS	Thickness Stardard Deviation (aparc.stats) of RightParsOpercularis
ST105CV	Cortical Volume (aparc.stats) of RightParsOrbitalis
ST105SA	Surface Area (aparc.stats) of RightParsOrbitalis
ST105TA	Thickness Average (aparc.stats) of RightParsOrbitalis
ST105TS	Thickness Stardard Deviation (aparc.stats) of RightParsOrbitalis
ST106CV	Cortical Volume (aparc.stats) of RightParsTriangularis
ST106SA	Surface Area (aparc.stats) of RightParsTriangularis
ST106TA	Thickness Average (aparc.stats) of RightParsTriangularis
ST106TS	Thickness Stardard Deviation (aparc.stats) of RightParsTriangularis
ST107CV	Cortical Volume (aparc.stats) of RightPericalcarine
ST107SA	Surface Area (aparc.stats) of RightPericalcarine
ST107TA	Thickness Average (aparc.stats) of RightPericalcarine
ST107TS	Thickness Stardard Deviation (aparc.stats) of RightPericalcarine
ST108CV	Cortical Volume (aparc.stats) of RightPostcentral
ST108SA	Surface Area (aparc.stats) of RightPostcentral
ST108TA	Thickness Average (aparc.stats) of RightPostcentral
ST108TS	Thickness Stardard Deviation (aparc.stats) of RightPostcentral
ST109CV	Cortical Volume (aparc.stats) of RightPosteriorCingulate
ST109SA	Surface Area (aparc.stats) of RightPosteriorCingulate
ST109TA	Thickness Average (aparc.stats) of RightPosteriorCingulate
ST109TS	Thickness Stardard Deviation (aparc.stats) of RightPosteriorCingulate
ST10CV	Cortical Volume (aparc.stats) of Icv
ST110CV	Cortical Volume (aparc.stats) of RightPrecentral
ST110SA	Surface Area (aparc.stats) of RightPrecentral
ST110TA	Thickness Average (aparc.stats) of RightPrecentral
ST110TS	Thickness Stardard Deviation (aparc.stats) of RightPrecentral

CODE	LABEL
ST111CV	Cortical Volume (aparc.stats) of RightPrecuneus
ST111SA	Surface Area (aparc.stats) of RightPrecuneus
ST111TA	Thickness Average (aparc.stats) of RightPrecuneus
ST111TS	Thickness Stardard Deviation (aparc.stats) of RightPrecuneus
ST112SV	Subcortical Volume (aseg.stats) of RightPutamen
ST113CV	Cortical Volume (aparc.stats) of RightRostralAnteriorCingulate
ST113SA	Surface Area (aparc.stats) of RightRostralAnteriorCingulate
ST113TA	Thickness Average (aparc.stats) of RightRostralAnteriorCingulate
ST113TS	Thickness Stardard Deviation (aparc.stats) of RightRostralAnteriorCingulate
ST114CV	Cortical Volume (aparc.stats) of RightRostralMiddleFrontal
ST114SA	Surface Area (aparc.stats) of RightRostralMiddleFrontal
ST114TA	Thickness Average (aparc.stats) of RightRostralMiddleFrontal
ST114TS	Thickness Stardard Deviation (aparc.stats) of RightRostralMiddleFrontal
ST115CV	Cortical Volume (aparc.stats) of RightSuperiorFrontal
ST115SA	Surface Area (aparc.stats) of RightSuperiorFrontal
ST115TA	Thickness Average (aparc.stats) of RightSuperiorFrontal
ST115TS	Thickness Stardard Deviation (aparc.stats) of RightSuperiorFrontal
ST116CV	Cortical Volume (aparc.stats) of RightSuperiorParietal
ST116SA	Surface Area (aparc.stats) of RightSuperiorParietal
ST116TA	Thickness Average (aparc.stats) of RightSuperiorParietal
ST116TS	Thickness Stardard Deviation (aparc.stats) of RightSuperiorParietal
ST117CV	Cortical Volume (aparc.stats) of RightSuperiorTemporal
ST117SA	Surface Area (aparc.stats) of RightSuperiorTemporal
ST117TA	Thickness Average (aparc.stats) of RightSuperiorTemporal
ST117TS	Thickness Stardard Deviation (aparc.stats) of RightSuperiorTemporal
ST118CV	Cortical Volume (aparc.stats) of RightSupramarginal
ST118SA	Surface Area (aparc.stats) of RightSupramarginal
ST118TA	Thickness Average (aparc.stats) of RightSupramarginal
ST118TS	Thickness Stardard Deviation (aparc.stats) of RightSupramarginal
ST119CV	Cortical Volume (aparc.stats) of RightTemporalPole
ST119SA	Surface Area (aparc.stats) of RightTemporalPole
ST119TA	Thickness Average (aparc.stats) of RightTemporalPole
ST119TS	Thickness Stardard Deviation (aparc.stats) of RightTemporalPole
ST11SV	Subcortical Volume (aseg.stats) of LeftAccumbensArea
ST120SV	Subcortical Volume (aseg.stats) of RightThalamus
ST121CV	Cortical Volume (aparc.stats) of RightTransverseTemporal
ST121SA	Surface Area (aparc.stats) of RightTransverseTemporal
ST121TA	Thickness Average (aparc.stats) of RightTransverseTemporal
ST121TS	Thickness Stardard Deviation (aparc.stats) of RightTransverseTemporal
ST124SV	Subcortical Volume (aseg.stats) of RightVentralDC
ST127SV	Subcortical Volume (aseg.stats) of ThirdVentricle
ST128SV	Subcortical Volume (aseg.stats) of WMHypoIntensities
ST129CV	Cortical Volume (aparc.stats) of LeftInsula

CODE	LABEL
ST129SA	Surface Area (aparc.stats) of LeftInsula
ST129TA	Thickness Average (aparc.stats) of LeftInsula
ST129TS	Thickness Stardard Deviation (aparc.stats) of LeftInsula
ST12SV	Subcortical Volume (aseg.stats) of LeftAmygdala
ST130CV	Cortical Volume (aparc.stats) of RightInsula
ST130SA	Surface Area (aparc.stats) of RightInsula
ST130TA	Thickness Average (aparc.stats) of RightInsula
ST130TS	Thickness Stardard Deviation (aparc.stats) of RightInsula
ST13CV	Cortical Volume (aparc.stats) of LeftBankssts
ST13SA	Surface Area (aparc.stats) of LeftBankssts
ST13TA	Thickness Average (aparc.stats) of LeftBankssts
ST13TS	Thickness Stardard Deviation (aparc.stats) of LeftBankssts
ST147SV	Subcortical Volume (aseg.stats) of LeftCorticalGM
ST148SV	Subcortical Volume (aseg.stats) of RightCorticalGM
ST149SV	Subcortical Volume (aseg.stats) of CorticalGM
ST14CV	Cortical Volume (aparc.stats) of LeftCaudalAnteriorCingulate
ST14SA	Surface Area (aparc.stats) of LeftCaudalAnteriorCingulate
ST14TA	Thickness Average (aparc.stats) of LeftCaudalAnteriorCingulate
ST14TS	Thickness Stardard Deviation (aparc.stats) of LeftCaudalAnteriorCingulate
ST150SV	Subcortical Volume (aseg.stats) of LeftCorticalWM
ST151SV	Subcortical Volume (aseg.stats) of RightCorticalWM
ST152SV	Subcortical Volume (aseg.stats) of CorticalWM
ST153SV	Subcortical Volume (aseg.stats) of SubcorticalGM
ST154SV	Subcortical Volume (aseg.stats) of TotalGM
ST155SV	Subcortical Volume (aseg.stats) of SupraTentorial
ST15CV	Cortical Volume (aparc.stats) of LeftCaudalMiddleFrontal
ST15SA	Surface Area (aparc.stats) of LeftCaudalMiddleFrontal
ST15TA	Thickness Average (aparc.stats) of LeftCaudalMiddleFrontal
ST15TS	Thickness Stardard Deviation (aparc.stats) of LeftCaudalMiddleFrontal
ST16SV	Subcortical Volume (aseg.stats) of LeftCaudate
ST17SV	Subcortical Volume (aseg.stats) of LeftCerebellumCortex
ST18SV	Subcortical Volume (aseg.stats) of LeftCerebellumWM
ST1SV	Subcortical Volume (aseg.stats) of Brainstem
ST21SV	Subcortical Volume (aseg.stats) of LeftChoroidPlexus
ST23CV	Cortical Volume (aparc.stats) of LeftCuneus
ST23SA	Surface Area (aparc.stats) of LeftCuneus
ST23TA	Thickness Average (aparc.stats) of LeftCuneus
ST23TS	Thickness Stardard Deviation (aparc.stats) of LeftCuneus
ST24CV	Cortical Volume (aparc.stats) of LeftEntorhinal
ST24SA	Surface Area (aparc.stats) of LeftEntorhinal
ST24TA	Thickness Average (aparc.stats) of LeftEntorhinal
ST24TS	Thickness Stardard Deviation (aparc.stats) of LeftEntorhinal
ST25CV	Cortical Volume (aparc.stats) of LeftFrontalPole

CODE	LABEL
ST25SA	Surface Area (aparc.stats) of LeftFrontalPole
ST25TA	Thickness Average (aparc.stats) of LeftFrontalPole
ST25TS	Thickness Stardard Deviation (aparc.stats) of LeftFrontalPole
ST26CV	Cortical Volume (aparc.stats) of LeftFusiform
ST26SA	Surface Area (aparc.stats) of LeftFusiform
ST26TA	Thickness Average (aparc.stats) of LeftFusiform
ST26TS	Thickness Stardard Deviation (aparc.stats) of LeftFusiform
ST28SA	Surface Area (aparc.stats) of LeftHemisphereWM
ST29SV	Subcortical Volume (aseg.stats) of LeftHippocampus
ST2SV	Subcortical Volume (aseg.stats) of CorpusCallosumAnterior
ST30SV	Subcortical Volume (aseg.stats) of LeftInferiorLateralVentricle
ST31CV	Cortical Volume (aparc.stats) of LeftInferiorParietal
ST31SA	Surface Area (aparc.stats) of LeftInferiorParietal
ST31TA	Thickness Average (aparc.stats) of LeftInferiorParietal
ST31TS	Thickness Stardard Deviation (aparc.stats) of LeftInferiorParietal
ST32CV	Cortical Volume (aparc.stats) of LeftInferiorTemporal
ST32SA	Surface Area (aparc.stats) of LeftInferiorTemporal
ST32TA	Thickness Average (aparc.stats) of LeftInferiorTemporal
ST32TS	Thickness Stardard Deviation (aparc.stats) of LeftInferiorTemporal
ST34CV	Cortical Volume (aparc.stats) of LeftIsthmusCingulate
ST34SA	Surface Area (aparc.stats) of LeftIsthmusCingulate
ST34TA	Thickness Average (aparc.stats) of LeftIsthmusCingulate
ST34TS	Thickness Stardard Deviation (aparc.stats) of LeftIsthmusCingulate
ST35CV	Cortical Volume (aparc.stats) of LeftLateralOccipital
ST35SA	Surface Area (aparc.stats) of LeftLateralOccipital
ST35TA	Thickness Average (aparc.stats) of LeftLateralOccipital
ST35TS	Thickness Stardard Deviation (aparc.stats) of LeftLateralOccipital
ST36CV	Cortical Volume (aparc.stats) of LeftLateralOrbitofrontal
ST36SA	Surface Area (aparc.stats) of LeftLateralOrbitofrontal
ST36TA	Thickness Average (aparc.stats) of LeftLateralOrbitofrontal
ST36TS	Thickness Stardard Deviation (aparc.stats) of LeftLateralOrbitofrontal
ST37SV	Subcortical Volume (aseg.stats) of LeftLateralVentricle
ST38CV	Cortical Volume (aparc.stats) of LeftLingual
ST38SA	Surface Area (aparc.stats) of LeftLingual
ST38TA	Thickness Average (aparc.stats) of LeftLingual
ST38TS	Thickness Stardard Deviation (aparc.stats) of LeftLingual
ST39CV	Cortical Volume (aparc.stats) of LeftMedialOrbitofrontal
ST39SA	Surface Area (aparc.stats) of LeftMedialOrbitofrontal
ST39TA	Thickness Average (aparc.stats) of LeftMedialOrbitofrontal
ST39TS	Thickness Stardard Deviation (aparc.stats) of LeftMedialOrbitofrontal
ST3SV	Subcortical Volume (aseg.stats) of CorpusCallosumCentral
ST40CV	Cortical Volume (aparc.stats) of LeftMiddleTemporal
ST40SA	Surface Area (aparc.stats) of LeftMiddleTemporal

CODE	LABEL
ST40TA	Thickness Average (aparc.stats) of LeftMiddleTemporal
ST40TS	Thickness Stardard Deviation (aparc.stats) of LeftMiddleTemporal
ST42SV	Subcortical Volume (aseg.stats) of LeftPallidum
ST43CV	Cortical Volume (aparc.stats) of LeftParacentral
ST43SA	Surface Area (aparc.stats) of LeftParacentral
ST43TA	Thickness Average (aparc.stats) of LeftParacentral
ST43TS	Thickness Stardard Deviation (aparc.stats) of LeftParacentral
ST44CV	Cortical Volume (aparc.stats) of LeftParahippocampal
ST44SA	Surface Area (aparc.stats) of LeftParahippocampal
ST44TA	Thickness Average (aparc.stats) of LeftParahippocampal
ST44TS	Thickness Stardard Deviation (aparc.stats) of LeftParahippocampal
ST45CV	Cortical Volume (aparc.stats) of LeftParsOpercularis
ST45SA	Surface Area (aparc.stats) of LeftParsOpercularis
ST45TA	Thickness Average (aparc.stats) of LeftParsOpercularis
ST45TS	Thickness Stardard Deviation (aparc.stats) of LeftParsOpercularis
ST46CV	Cortical Volume (aparc.stats) of LeftParsOrbitalis
ST46SA	Surface Area (aparc.stats) of LeftParsOrbitalis
ST46TA	Thickness Average (aparc.stats) of LeftParsOrbitalis
ST46TS	Thickness Stardard Deviation (aparc.stats) of LeftParsOrbitalis
ST47CV	Cortical Volume (aparc.stats) of LeftParsTriangularis
ST47SA	Surface Area (aparc.stats) of LeftParsTriangularis
ST47TA	Thickness Average (aparc.stats) of LeftParsTriangularis
ST47TS	Thickness Stardard Deviation (aparc.stats) of LeftParsTriangularis
ST48CV	Cortical Volume (aparc.stats) of LeftPericalcarine
ST48SA	Surface Area (aparc.stats) of LeftPericalcarine
ST48TA	Thickness Average (aparc.stats) of LeftPericalcarine
ST48TS	Thickness Stardard Deviation (aparc.stats) of LeftPericalcarine
ST49CV	Cortical Volume (aparc.stats) of LeftPostcentral
ST49SA	Surface Area (aparc.stats) of LeftPostcentral
ST49TA	Thickness Average (aparc.stats) of LeftPostcentral
ST49TS	Thickness Stardard Deviation (aparc.stats) of LeftPostcentral
ST4SV	Subcortical Volume (aseg.stats) of CorpusCallosumMidAnterior
ST50CV	Cortical Volume (aparc.stats) of LeftPosteriorCingulate
ST50SA	Surface Area (aparc.stats) of LeftPosteriorCingulate
ST50TA	Thickness Average (aparc.stats) of LeftPosteriorCingulate
ST50TS	Thickness Stardard Deviation (aparc.stats) of LeftPosteriorCingulate
ST51CV	Cortical Volume (aparc.stats) of LeftPrecentral
ST51SA	Surface Area (aparc.stats) of LeftPrecentral
ST51TA	Thickness Average (aparc.stats) of LeftPrecentral
ST51TS	Thickness Stardard Deviation (aparc.stats) of LeftPrecentral
ST52CV	Cortical Volume (aparc.stats) of LeftPrecuneus
ST52SA	Surface Area (aparc.stats) of LeftPrecuneus
ST52TA	Thickness Average (aparc.stats) of LeftPrecuneus

CODE	LABEL
ST52TS	Thickness Stardard Deviation (aparc.stats) of LeftPrecuneus
ST53SV	Subcortical Volume (aseg.stats) of LeftPutamen
ST54CV	Cortical Volume (aparc.stats) of LeftRostralAnteriorCingulate
ST54SA	Surface Area (aparc.stats) of LeftRostralAnteriorCingulate
ST54TA	Thickness Average (aparc.stats) of LeftRostralAnteriorCingulate
ST54TS	Thickness Stardard Deviation (aparc.stats) of LeftRostralAnteriorCingulate
ST55CV	Cortical Volume (aparc.stats) of LeftRostralMiddleFrontal
ST55SA	Surface Area (aparc.stats) of LeftRostralMiddleFrontal
ST55TA	Thickness Average (aparc.stats) of LeftRostralMiddleFrontal
ST55TS	Thickness Stardard Deviation (aparc.stats) of LeftRostralMiddleFrontal
ST56CV	Cortical Volume (aparc.stats) of LeftSuperiorFrontal
ST56SA	Surface Area (aparc.stats) of LeftSuperiorFrontal
ST56TA	Thickness Average (aparc.stats) of LeftSuperiorFrontal
ST56TS	Thickness Stardard Deviation (aparc.stats) of LeftSuperiorFrontal
ST57CV	Cortical Volume (aparc.stats) of LeftSuperiorParietal
ST57SA	Surface Area (aparc.stats) of LeftSuperiorParietal
ST57TA	Thickness Average (aparc.stats) of LeftSuperiorParietal
ST57TS	Thickness Stardard Deviation (aparc.stats) of LeftSuperiorParietal
ST58CV	Cortical Volume (aparc.stats) of LeftSuperiorTemporal
ST58SA	Surface Area (aparc.stats) of LeftSuperiorTemporal
ST58TA	Thickness Average (aparc.stats) of LeftSuperiorTemporal
ST58TS	Thickness Stardard Deviation (aparc.stats) of LeftSuperiorTemporal
ST59CV	Cortical Volume (aparc.stats) of LeftSupramarginal
ST59SA	Surface Area (aparc.stats) of LeftSupramarginal
ST59TA	Thickness Average (aparc.stats) of LeftSupramarginal
ST59TS	Thickness Stardard Deviation (aparc.stats) of LeftSupramarginal
ST5SV	Subcortical Volume (aseg.stats) of CorpusCallosumMidPosterior
ST60CV	Cortical Volume (aparc.stats) of LeftTemporalPole
ST60SA	Surface Area (aparc.stats) of LeftTemporalPole
ST60TA	Thickness Average (aparc.stats) of LeftTemporalPole
ST60TS	Thickness Stardard Deviation (aparc.stats) of LeftTemporalPole
ST61SV	Subcortical Volume (aseg.stats) of LeftThalamus
ST62CV	Cortical Volume (aparc.stats) of LeftTransverseTemporal
ST62SA	Surface Area (aparc.stats) of LeftTransverseTemporal
ST62TA	Thickness Average (aparc.stats) of LeftTransverseTemporal
ST62TS	Thickness Stardard Deviation (aparc.stats) of LeftTransverseTemporal
ST65SV	Subcortical Volume (aseg.stats) of LeftVentralDC
ST69SV	Subcortical Volume (aseg.stats) of OpticChiasm
ST6SV	Subcortical Volume (aseg.stats) of CorpusCallosumPosterior
ST70SV	Subcortical Volume (aseg.stats) of RightAccumbensArea
ST71SV	Subcortical Volume (aseg.stats) of RightAmygdala
ST72CV	Cortical Volume (aparc.stats) of RightBankssts
ST72SA	Surface Area (aparc.stats) of RightBankssts

CODE	LABEL
ST72TA	Thickness Average (aparc.stats) of RightBankssts
ST72TS	Thickness Stardard Deviation (aparc.stats) of RightBankssts
ST73CV	Cortical Volume (aparc.stats) of RightCaudalAnteriorCingulate
ST73SA	Surface Area (aparc.stats) of RightCaudalAnteriorCingulate
ST73TA	Thickness Average (aparc.stats) of RightCaudalAnteriorCingulate
ST73TS	Thickness Stardard Deviation (aparc.stats) of RightCaudalAnteriorCingulate
ST74CV	Cortical Volume (aparc.stats) of RightCaudalMiddleFrontal
ST74SA	Surface Area (aparc.stats) of RightCaudalMiddleFrontal
ST74TA	Thickness Average (aparc.stats) of RightCaudalMiddleFrontal
ST74TS	Thickness Stardard Deviation (aparc.stats) of RightCaudalMiddleFrontal
ST75SV	Subcortical Volume (aseg.stats) of RightCaudate
ST76SV	Subcortical Volume (aseg.stats) of RightCerebellumCortex
ST77SV	Subcortical Volume (aseg.stats) of RightCerebellumWM
ST7SV	Subcortical Volume (aseg.stats) of Csf
ST80SV	Subcortical Volume (aseg.stats) of RightChoroidPlexus
ST82CV	Cortical Volume (aparc.stats) of RightCuneus
ST82SA	Surface Area (aparc.stats) of RightCuneus
ST82TA	Thickness Average (aparc.stats) of RightCuneus
ST82TS	Thickness Stardard Deviation (aparc.stats) of RightCuneus
ST83CV	Cortical Volume (aparc.stats) of RightEntorhinal
ST83SA	Surface Area (aparc.stats) of RightEntorhinal
ST83TA	Thickness Average (aparc.stats) of RightEntorhinal
ST83TS	Thickness Stardard Deviation (aparc.stats) of RightEntorhinal
ST84CV	Cortical Volume (aparc.stats) of RightFrontalPole
ST84SA	Surface Area (aparc.stats) of RightFrontalPole
ST84TA	Thickness Average (aparc.stats) of RightFrontalPole
ST84TS	Thickness Stardard Deviation (aparc.stats) of RightFrontalPole
ST85CV	Cortical Volume (aparc.stats) of RightFusiform
ST85SA	Surface Area (aparc.stats) of RightFusiform
ST85TA	Thickness Average (aparc.stats) of RightFusiform
ST85TS	Thickness Stardard Deviation (aparc.stats) of RightFusiform
ST88SV	Subcortical Volume (aseg.stats) of RightHippocampus
ST89SV	Subcortical Volume (aseg.stats) of RightInferiorLateralVentricle
ST8SV	Subcortical Volume (aseg.stats) of FifthVentricle
ST90CV	Cortical Volume (aparc.stats) of RightInferiorParietal
ST90SA	Surface Area (aparc.stats) of RightInferiorParietal
ST90TA	Thickness Average (aparc.stats) of RightInferiorParietal
ST90TS	Thickness Stardard Deviation (aparc.stats) of RightInferiorParietal
ST91CV	Cortical Volume (aparc.stats) of RightInferiorTemporal
ST91SA	Surface Area (aparc.stats) of RightInferiorTemporal
ST91TA	Thickness Average (aparc.stats) of RightInferiorTemporal
ST91TS	Thickness Stardard Deviation (aparc.stats) of RightInferiorTemporal
ST93CV	Cortical Volume (aparc.stats) of RightIsthmusCingulate

CODE	LABEL
ST93SA	Surface Area (aparc.stats) of RightIsthmusCingulate
ST93TA	Thickness Average (aparc.stats) of RightIsthmusCingulate
ST93TS	Thickness Stardard Deviation (aparc.stats) of RightIsthmusCingulate
ST94CV	Cortical Volume (aparc.stats) of RightLateralOccipital
ST94SA	Surface Area (aparc.stats) of RightLateralOccipital
ST94TA	Thickness Average (aparc.stats) of RightLateralOccipital
ST94TS	Thickness Stardard Deviation (aparc.stats) of RightLateralOccipital
ST95CV	Cortical Volume (aparc.stats) of RightLateralOrbitofrontal
ST95SA	Surface Area (aparc.stats) of RightLateralOrbitofrontal
ST95TA	Thickness Average (aparc.stats) of RightLateralOrbitofrontal
ST95TS	Thickness Stardard Deviation (aparc.stats) of RightLateralOrbitofrontal
ST96SV	Subcortical Volume (aseg.stats) of RightLateralVentricle
ST97CV	Cortical Volume (aparc.stats) of RightLingual
ST97SA	Surface Area (aparc.stats) of RightLingual
ST97TA	Thickness Average (aparc.stats) of RightLingual
ST97TS	Thickness Stardard Deviation (aparc.stats) of RightLingual
ST98CV	Cortical Volume (aparc.stats) of RightMedialOrbitofrontal
ST98SA	Surface Area (aparc.stats) of RightMedialOrbitofrontal
ST98TA	Thickness Average (aparc.stats) of RightMedialOrbitofrontal
ST98TS	Thickness Stardard Deviation (aparc.stats) of RightMedialOrbitofrontal
ST99CV	Cortical Volume (aparc.stats) of RightMiddleTemporal
ST99SA	Surface Area (aparc.stats) of RightMiddleTemporal
ST99TA	Thickness Average (aparc.stats) of RightMiddleTemporal
ST99TS	Thickness Stardard Deviation (aparc.stats) of RightMiddleTemporal

Table E3

Average Sum of Absolute Differences (SAD) and Mean Absolute Error (MAE)

Method	AVG_SAD	AVG_MAE	AVG_SAD_NORM	AVG_MAE_NORM
MissForest	908.555778	3.867489	30.432037	0.129525
Iterative	1002.212996	4.266194	34.209244	0.145602
MICEForest	1136.696087	4.838547	36.837011	0.156785

Notes. Metrics are shown for both raw and normalised data. Lower values indicate better imputation accuracy.

Table E4

Top 152 highest ranking features based on 70% cumulative importance (MDI method)

Feature	Mean Importance	SD Importance
Q4SCORE	0.025173	0.006005
Q7SCORE	0.024474	0.006817
TRABSCOR	0.023359	0.007361
Q1SCORE	0.019295	0.00614
NPIETOT	0.019173	0.006227
TRAASCOR	0.013611	0.005027
CATANIMSC	0.012682	0.004557
ST91CV_norm	0.011111	0.004307
ST71SV_norm	0.010558	0.004505
Q8SCORE	0.010215	0.004911
AVDELTOT	0.009297	0.004032
ST83TA	0.008657	0.003818
NPIITOT	0.00862	0.004144
ST91TA	0.008297	0.003896
ST24TA	0.007283	0.003323
ST55CV_norm	0.006963	0.002861
NPIGTOT	0.00691	0.003306
ST90CV_norm	0.006673	0.002929
NPICTOT	0.006596	0.003671
Q13SCORE	0.006584	0.003616
ST99TA	0.006413	0.0028
ST12SV_norm	0.00639	0.002701
ST99CV_norm	0.006256	0.002239
ST32SA_norm	0.006067	0.003111
ST55SA_norm	0.005733	0.002405
NPIDTOT	0.005542	0.002675
ST40CV_norm	0.005486	0.002584
ST83CV_norm	0.005226	0.002505
ST85CV_norm	0.005165	0.002516
ST72CV_norm	0.005087	0.002229
ST32CV_norm	0.004951	0.001993
ST70SV_norm	0.004834	0.00282
ST34CV_norm	0.004637	0.002447
ST40TA	0.004467	0.001671
ST90SA_norm	0.004465	0.002048
ST91SA_norm	0.00445	0.002076
CLOCKSCOR	0.004389	0.002906
ST29SV_norm	0.004332	0.002327
ST72TA	0.004295	0.001715
AVTOTB	0.00425	0.002263

Feature	Mean Importance	SD Importance
ST85SA_norm	0.004179	0.001984
ST14CV_norm	0.004107	0.001873
ST14SA_norm	0.00406	0.001614
ST73SA_norm	0.004005	0.001434
ST113SA_norm	0.00397	0.001569
ST117TA	0.003941	0.001924
ST50SA_norm	0.003846	0.001864
ST119TA	0.003796	0.0016
ST50CV_norm	0.003756	0.001863
ST40SA_norm	0.003749	0.001689
ST88SV_norm	0.003717	0.001471
ST13SA_norm	0.003651	0.001572
ST26SA_norm	0.003632	0.001506
ST73CV_norm	0.003631	0.001342
ST15CV_norm	0.003619	0.001527
ST118CV_norm	0.00361	0.001786
ST30SV_norm	0.003609	0.001259
ST13CV_norm	0.003606	0.001417
ST42SV_norm	0.003594	0.001419
ST117CV_norm	0.00357	0.001497
ST118SA_norm	0.003568	0.001596
ST62TA	0.003563	0.001168
ST26CV_norm	0.003554	0.001646
ST34TA	0.003534	0.001459
ST24CV_norm	0.00353	0.001846
ST103TA	0.003516	0.001109
ST89SV_norm	0.003503	0.001423
ST113CV_norm	0.003494	0.001292
ST15SA_norm	0.003452	0.001179
ST90TA	0.003447	0.001149
ST155SV_norm	0.003438	0.00157
ST107TA	0.003421	0.000801
ST72SA_norm	0.003417	0.001436
ST58TA	0.003406	0.001454
ST153SV_norm	0.003397	0.001744
ST85TA	0.003396	0.001123
ST21SV_norm	0.003382	0.001307
ST23SA_norm	0.003374	0.001439
ST54CV_norm	0.003322	0.001243
ST48SA_norm	0.003292	0.001237
ST128SV_norm	0.00329	0.001151
ST48CV_norm	0.003289	0.001072
ST121TA	0.003287	0.00115
ST109TA	0.003271	0.001241
ST23CV_norm	0.003256	0.001128

Feature	Mean Importance	SD Importance
ST82TA	0.003244	0.001127
ST130TA	0.003241	0.001158
ST73TA	0.00321	0.001054
ST32TA	0.003201	0.001019
ST106TA	0.003188	0.000866
ST94TA	0.003187	0.001121
ST26TA	0.003186	0.001124
NPIJTOT	0.003177	0.00202
ST99SA_norm	0.003144	0.001441
ST31CV_norm	0.003144	0.001215
ST56SA_norm	0.003128	0.001434
Q5SCORE	0.003127	0.002341
ST11SV_norm	0.003107	0.001356
ST103SA_norm	0.003095	0.001088
ST109CV_norm	0.003051	0.001242
ST114SA_norm	0.003011	0.001012
ST37SV_norm	0.002994	0.000984
ST148SV_norm	0.002985	0.001504
ST104TA	0.002974	0.000836
ST105TA	0.002968	0.000913
ST44TA	0.002957	0.000777
ST119CV_norm	0.002957	0.000736
ST45TA	0.00295	0.00079
ST69SV_norm	0.002946	0.000928
ST51SA_norm	0.002888	0.000879
ST116CV_norm	0.002887	0.001125
ST80SV_norm	0.002876	0.000999
ST1SV_norm	0.002873	0.001208
ST54SA_norm	0.002873	0.00083
ST113TA	0.00285	0.00086
ST111CV_norm	0.002846	0.001202
ST50TA	0.002839	0.000918
ST115SA_norm	0.002833	0.000978
ST43TA	0.002832	0.000875
ST77SV_norm	0.002818	0.000749
ST60TA	0.002806	0.001008
ST9SV_norm	0.002806	0.000811
ST103CV_norm	0.002798	0.001074
ST118TA	0.002793	0.000762
ST95TA	0.002793	0.001007
ST60CV_norm	0.002791	0.000727
ST108TA	0.002788	0.001059
ST35TA	0.002773	0.000708
ST130SA_norm	0.002772	0.000945
ST31SA_norm	0.002771	0.001168

Feature	Mean Importance	SD Importance
ST59TA	0.002765	0.000941
ST93TA	0.002759	0.00104
ST121SA_norm	0.002758	0.000783
ST25TA	0.002757	0.0008
ST84TA	0.002742	0.000743
ST54TA	0.002741	0.00077
ST10CV	0.00273	0.000788
ST56TA	0.002728	0.000792
ST84SA_norm	0.002723	0.000926
ST129TA	0.002723	0.000821
ST98TA	0.002721	0.000783
ST46TA	0.002719	0.00094
ST101SV_norm	0.002716	0.000978
ST107CV_norm	0.002694	0.000829
ST97CV_norm	0.002683	0.000797
ST34SA_norm	0.002681	0.001102
ST74SA_norm	0.00268	0.000905
ST102SA_norm	0.002677	0.000769
ST51TA	0.002667	0.000826
ST16SV_norm	0.00266	0.00075
ST102CV_norm	0.00266	0.000766
ST49SA_norm	0.002655	0.000843

Appendix F

Supplementary material of chapter 8 (Study 5)

Participant Information Sheet (co-design)

Name of department: **Psychological Sciences and Health**

Title of the study: **Development of a new digital monitoring tool for behavioural symptoms of dementia**

Investigators: **Dr William McGeown (Chief Investigator), Sara Scarfo, Dr Yashar Moshfeghi**

Please read this document before deciding to participate. If you have any questions, please ask in person or via email or phone using the details below.

Researchers: Sara Scarfo - PhD student researcher; Dr William McGeown – Chief investigator and supervisor, Dr Yashar Moshfeghi – second supervisor.

What is the purpose of this research?

The aim of this research is to co-develop and test a new digital tool to monitor the frequency, intensity, and associated distress of behavioural symptoms that might occur during the course of dementia. Understanding the occurrence of these symptoms will be of importance to advance the research, as it will help in the development of new interventions.

Do you have to take part?

No, the participation in this research study is voluntary. You are free to refuse or withdraw from participation at any time, without giving reasons and without penalty.

What will you do in the project?

The research will consist of three parts:

The first appointment will be a group session, which will last approximately 2 hours: in this session, you will take part in a focus group consisting of the researcher and approximately four other caregivers (if you should not be available to join the focus group on the date arranged, an individual in-person or telephone/video appointment will be offered instead). On this occasion, you will be shown a first draft of the new digital monitoring tool, and you will be asked to join in a conversation about different aspects of this (e.g., the clarity of the instruction manual, the suitability of the questions asked,

the ways used to submit answers to the questions, and you can provide additional ideas that were not previously considered by the researcher). This session will be audio-recorded, so the researcher will be able to create anonymous transcripts, which will be used to integrate the feedback of the focus group to the new version of the tool. This session will be held either at the University of Strathclyde, or over a digital platform (e.g., Zoom) if this is the group's preferred choice. If at the University, a reimbursement of up to £40 will be available for time reimbursement and travel expenses (if online, a reimbursement of £20 can be provided).

In the second phase, you will be asked to trial the new, co-developed short digital questionnaire every day (this should take approximately 5 minutes to complete), for the duration of a month. It is with this digital tool that you will report on the daily behaviour of the person with dementia. I will get in touch after two weeks, over the phone, to collect feedback and answer any queries (although you can contact us at any time).

At the end of the month, a survey will be sent to collect your individual feedback on the experience of using the tool, and after this, a second focus-group will be arranged, which will last approximately 1 hour (if you should not be available to join the focus group on the date arranged, an individual in-person or telephone appointment will be offered instead): during this, you will be asked to join in a conversation on the experience of using of the tool; this session as well will be audio-recorded, so the researcher will be able to create anonymous transcripts, which will be used to integrate the feedback of the focus group to the digital monitoring tool. This session will be held either at the University of Strathclyde, or over a digital platform (e.g., Zoom) if this is the group's preferred choice. If at the University, a reimbursement of up to £40 will be available for time reimbursement and travel expenses (if online, a reimbursement of £20 can be provided).

Why have you been invited to take part?

You are invited to participate if you are, or have been, the caregiver of a person formally diagnosed with dementia. You also need to be:

- Aged 18+;
- Able to speak, read and understand English language (the assessment will be in English);
- Free from visual impairment (once correction with glasses has been considered) that would affect use of the digital tool;
- You should not have any neurological/psychiatric conditions which affect cognition.

What are the potential risks to taking part?

Risk of infection from Covid-19 has been assessed, as the research involves face-to-face appointments; the researcher will prevent this by making use of PPE according to governmental regulations. If the researcher or the participant is unwell, the session will be moved to a later date.

What information is being collected in the project?

Your personal details (name, address, contact number, email address), and study data (records collected through the digital tool, audio recordings of the focus groups, and feedback on the research) will be collected. A code will be used to link the personal details with the study data, in order to make it anonymous.

Who will have access to the information?

Only the researcher and chief investigator will have access to your personal information. The study data (e.g., questionnaire responses, feedback on the digital tool) will be anonymised (will not contain any identifiable information), and this along with any derived data, will be shared among the investigator team and will potentially be made available on public repositories.

Where will the information be stored and how long will it be kept for?

Your personal details (e.g. name, address, contact number) and study data (e.g. digital tool reporting, questionnaire responses, feedback) will be stored securely. Your personal data will be treated confidentially, will be stored only as long as necessary, and will not be shared outside of the research team. Audio files from the focus groups will be destroyed after transcription. Your anonymous study data will be stored indefinitely, may be used in future studies, or may be provided to those outside the research team.

You may request that your data is destroyed (but please note that it will not be possible to remove your data once it has been combined with that from other participants). Please note that you have the option of having your personal and/or behavioural data destroyed. If you wish to withdraw any aspect of your data in future, please contact william.mcgeown@strath.ac.uk.

The University of Strathclyde is registered with the Information Commissioner's Office. All personal data on participants will be processed in accordance with the provisions of the General Data Protection Regulation (EU) 2016/679. Please read our Privacy Notice for Research Participants for more information about your rights under the legislation.

Thank you for reading this information – please ask any questions if you are unsure about what is written here.

What happens next?

If you have decided to participate, thank you, please sign the consent form.

If you decided not to participate, thank you for your time and interest.

Researcher contact details:
Researcher: Sara Scarfo
Status: PhD student
Institution: University of Strathclyde

Chief Investigator contact details:
Name: Dr William McGeown

Telephone: 07595889693
Email:
sara.scarfo.2020@uni.strath.ac.uk

Status: Reader
School of Psychological Sciences & Health,
University of Strathclyde,
Graham Hills Building,
40 George Street, Glasgow.
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E-mail: william.mcgeown@strath.ac.uk

This research was granted ethical approval by the University of Strathclyde Ethics Committee.

If you have any questions/concerns, during or after the research, or wish to contact an independent person to whom any questions may be directed or further information may be sought from, please contact:

Secretary to the University Ethics Committee
Research & Knowledge Exchange Services
University of Strathclyde
Graham Hills Building
50 George Street
Glasgow
G1 1QE

Telephone: 0141 548 3707
Email: ethics@strath.ac.uk

Participant Information Sheet (pilot - caregiver)

Name of department: **Psychological Sciences and Health**

Title of the study: **Development of a new digital monitoring tool for behavioural symptoms of dementia**

Investigators: **Dr William McGeown (Chief Investigator), Sara Scarfo, Dr Yashar Moshfeghi**

Please read this document before deciding to participate. If you have any questions, please ask in person or via email or phone using the details below.

Researchers: Sara Scarfo - PhD student researcher; Dr William McGeown – Chief investigator and supervisor, Dr Yashar Moshfeghi – second supervisor.

What is the purpose of this research?

The aim of this research is to develop and test a new digital tool to monitor the frequency, intensity, and associated distress of behavioural symptoms that might occur during the course of dementia. Understanding the occurrence of these symptoms will be of importance to advance the research, as it will help in the development of new interventions.

Do you have to take part?

No, the participation in this research study is voluntary. You are free to refuse or withdraw from participation at any time, without giving reasons and without penalty.

What will you do in the project?

The research will consist of three parts:

The first, in-person session will last approximately 2 hours: in this session, the participant with dementia will be asked to complete some neuropsychological assessment tests, which will cover memory, language, attention, drawing ability, everyday abilities, etc. You (the caregiver) will be asked some additional information, and will be instructed on the use of the new digital monitoring tool. This session will be held either at the University of Strathclyde, or at your home if this is your preferred choice

In the second part of the study, you will be asked to complete a short digital questionnaire every day (this should take approximately 5 minutes to complete), for the duration of a month. It is with this digital tool that you will report on the daily behaviour

of the person with dementia. I will get in touch after two weeks, over the phone, to collect feedback and answer any queries (although you can contact us at any time).

At the end of the month, a survey will be sent to collect some feedback on the experience of using the tool, and after this, a final in-person or telephone session will be arranged, which will last approximately 1 hour: during this, you will be asked to complete an interview, and we will ask for feedback on your experience of participation in the study to both participants.

Why have you been invited to take part?

You are invited to participate if you are the caregiver of a person formally diagnosed with dementia. You also need to be:

- Aged 18+;
- Able to speak, read and understand English language (the assessment will be in English);
- Free from visual impairment (once correction with glasses has been considered) that would affect use of the digital tool;
- You should not have any neurological/psychiatric conditions which affect cognition.

What are the potential risks to taking part?

For the behavioural tests, breaks will be provided if the participant (person with dementia) gets tired or anxious. They may find some tests more difficult than others, but they will be reassured not to worry, and to try their best.

Please note that this study does not constitute a “health check” and no individual feedback on the assessments will be provided. This is because such feedback outside of the normal clinical setting is of questionable value, and might even be harmful (for example, causing undue alarm and having potentially adverse effects on insurance status), especially when given without prior counselling or support.

For you (the caregiver), completing the new assessment tool daily might prove challenging, both for the frequency of completion and for the nature of the questions, which involve the disclosure of the symptoms the participant diagnosed with dementia might be experiencing on a daily basis. There will be the opportunity to discuss this with us at any time during participation in the research.

Risk of infection from Covid-19 has been assessed, as the research involves face-to-face appointments; the researcher will prevent this by performing a lateral-flow test prior to every face-to-face appointment, and they will make use of PPE according to governmental regulations.

What information is being collected in the project?

Your personal details (name, address, contact number, email address), and study data (questionnaires reporting on the person with dementia’s ability/behaviour, records

collected through the digital tool, and feedback on the research). A code will be used to link the personal details with the study data, in order to make it anonymous.
The person with dementia will be asked to undertake neuropsychological tests (e.g., for memory, attention, language, drawing ability) and these will be retained again using a code.

Who will have access to the information?

Only the researcher and chief investigator will have access to your personal information. The study data (e.g., questionnaire responses, feedback on the digital tool) will be anonymised (will not contain any identifiable information) and this along with any derived data, will be shared among the investigator team and will potentially be made available on public repositories.

Where will the information be stored and how long will it be kept for?

Your personal details (e.g. name, address, contact number) and study data (e.g. digital tool reporting, questionnaire responses, feedback) will be stored securely. Your personal data will be treated confidentially, will be stored only as long as necessary, and will not be shared outside of the research team. Your anonymous study data will be stored indefinitely, may be used in future studies, or may be provided to those outside the research team.

You may request that your data is destroyed (but please note that it will not be possible to remove your data once it has been combined with that from other participants). Please note that you have the option of having your personal and/or behavioural data destroyed. If you wish to withdraw any aspect of your data in future, please contact william.mcgeown@strath.ac.uk

The University of Strathclyde is registered with the Information Commissioner's Office. All personal data on participants will be processed in accordance with the provisions of the General Data Protection Regulation (EU) 2016/679. Please read our Privacy Notice for Research Participants for more information about your rights under the legislation.

Thank you for reading this information – please ask any questions if you are unsure about what is written here.

What happens next?

If you have decided to participate, thank you, please sign the consent form. Please note that participation is voluntary (only a reimbursement of up to £40, which consists of £20 for time reimbursement and £20 for travel expenses, can be provided).

If you decided not to participate, thank you for your time and interest.

Researcher contact details:
Researcher: Sara Scarfo
Status: PhD student
Institution: University of Strathclyde
Telephone: 07595889693
Email:
sara.scarfo.2020@uni.strath.ac.uk

Chief Investigator contact details:
Name: Dr William McGeown
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School of Psychological Sciences & Health,
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40 George Street, Glasgow.
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Telephone: (0141) 548 4477
E-mail: william.mcgeown@strath.ac.uk

This research was granted ethical approval by the University of Strathclyde Ethics Committee.

If you have any questions/concerns, during or after the research, or wish to contact an independent person to whom any questions may be directed or further information may be sought from, please contact:

Secretary to the University Ethics Committee
Research & Knowledge Exchange Services
University of Strathclyde
Graham Hills Building
50 George Street
Glasgow
G1 1QE

Telephone: 0141 548 3707
Email: ethics@strath.ac.uk

Participant Information Sheet (Pilot - participant with dementia)

Name of department: **Psychological Sciences and Health**

Title of the study: **Development of a new digital monitoring tool for behavioural symptoms of dementia**

Investigators: **Dr William McGeown (Chief Investigator), Sara Scarfo, Dr Yashar Moshfeghi**

Please read this document before deciding to participate. If you have any questions, please ask in person, or via email or phone using the details below.

Researchers: Sara Scarfo - PhD student researcher; Dr William McGeown – Chief investigator and supervisor, Dr Yashar Moshfeghi – second supervisor.

What is the purpose of this research?

The aim of this research is to develop and test a new digital tool to monitor the frequency, intensity, and associated distress of behavioural symptoms that might occur during the course of dementia. Understanding the occurrence of these symptoms will be of importance to advance the research, as it will help in the development of new interventions.

Do you have to take part?

No, the participation in this research study is voluntary. You are free to refuse or withdraw from participation at any time, without giving reasons and without penalty.

What will you do in the project?

The research will consist of three parts:

The first, in-person session will last approximately 2 hours: here you will be asked to complete some short tests which will cover attention, language, memory, drawing ability, etc. In this session, your caregiver will be asked some further questions about you, and they will be instructed on the use of our new symptom monitoring tool. This session will be held either at the University of Strathclyde, or at your home if this is your preferred choice.

In the second part of the study, your caregiver will complete short questionnaires every day, answering questions about your symptoms. I will get in touch with the caregiver after two weeks, over the phone, to collect feedback and answer any queries you both may have.

At the end of the month, we will have a final conversation with your caregiver, who will be asked some additional questions about you, and we will ask for feedback from you and your caregiver, about the new tool and your experience of participation in the study.

Why have you been invited to take part?

You are invited to participate if you have received a formal diagnosis of dementia. You also need to be:

- Aged 18+;
- Able to speak, read and understand English language (the assessment will be in English);
- Free from visual/auditory impairment (once correction with glasses and hearing aids has been considered) that would affect performance on cognitive tasks;
- You should not have any neurological or psychiatric conditions other than dementia.

What are the potential risks to you in taking part?

For the behavioural tests, breaks will be provided if you get tired or anxious. You may find some tests more difficult than others, but they are designed this way, so please try not to worry, and try your best.

Please note that this study does not constitute a "health check" and no individual feedback on your assessments will be provided. This is because such feedback outside of the normal clinical setting is of questionable value.

Risk of infection from Covid-19 has been assessed, as the research involves face-to-face appointments; the researcher will prevent this by making use of PPE according to governmental regulations. If the researcher or the participant is unwell, the session will be moved to a later date.

What information is being collected in the project?

Your personal details (name, address, contact number, email address), and study data (neuropsychological assessments, records collected through the digital tool, and feedback on the research). A code will be used to link the personal details with the study data, in order to make it anonymous.

Who will have access to the information?

Only the researchers will have access to your personal information.

Data from the study and/or results (which will not contain any identifiable information) may be made public.

Where will the information be stored and how long will it be kept for?

Your data will be kept strictly confidential, anonymised, and any personal information will be kept no longer than necessary. Anonymised data will be retained for an indefinite period of time.

Please note that if you wish to have your personal and/or behavioural data destroyed, this is possible providing it has not been combined with the data from other participants. If you wish to withdraw any aspect of your data in future, please contact william.mcgeown@strath.ac.uk.

The University of Strathclyde is registered with the Information Commissioner's Office. All personal data on participants will be processed in accordance with the provisions of the General Data Protection Regulation (EU) 2016/679. Please read our Privacy Notice for Research Participants for more information about your rights under the legislation.

Thank you for reading this information – please ask any questions if you are unsure about what is written here.

What happens next?

If you have decided to participate, thank you, please sign the consent form. Please note that participation is voluntary (only a reimbursement of up to £40: which consists of £20 for time reimbursement and £20 for travel expenses can be provided).

If you decided not to participate, thank you for your time and interest.

Researcher contact details:
Researcher: Sara Scarfo
Status: PhD student
Institution: University of Strathclyde
Telephone: 07595889693
Email:
sara.scarfo.2020@uni.strath.ac.uk

Chief Investigator contact details:
Name: Dr William McGeown
Status: Reader
School of Psychological Sciences & Health,
University of Strathclyde,
Graham Hills Building,
40 George Street, Glasgow.
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Telephone: (0141) 548 4477
E-mail: william.mcgeown@strath.ac.uk

This research was granted ethical approval by the University of Strathclyde Ethics Committee.

If you have any questions/concerns, during or after the research, or wish to contact an independent person to whom any questions may be directed or further information may be sought from, please contact:

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50 George Street
Glasgow
G1 1QE

Telephone: 0141 548 3707
Email: ethics@strath.ac.uk

Consent Form (same for both components)

Name of department: **Psychological Sciences and Health**
Title of the study: **Development of a new digital monitoring tool for behavioural symptoms of dementia**

	Please initial here
I confirm that I have read and understood the Participant Information Sheet for the above project and the researcher has answered any queries to my satisfaction.	
I confirm that I have read and understood the Privacy Notice for Participants in Research Projects and understand how my personal information will be used and what will happen to it (i.e. how it will be stored and for how long).	
I understand that my participation is voluntary and that I am free to withdraw from the project at any time, up to the point of completion, without having to give a reason and without any consequences.	
I understand that I can request that my data is destroyed at any time in the future (personal data: including name, contact information, address; or study data: e.g., questionnaire responses, digital tool feedback). If requested, although the researchers would securely dispose of my data and would not use it for further analyses, I note that withdrawal of my data would not be possible from analyses that had already been conducted (e.g., once my data had been integrated with data from other participants).	
I understand that any information recorded in the research will remain confidential and no information that identifies me will be made publicly available.	
I understand that my anonymous data may be shared with those outside the research team (without the inclusion of personal identifying information).	
I consent to the sessions being audio-recorded.	
I consent to being a participant in the project.	

Please tick the box and provide your email address if you wish to receive feedback about the overall outcomes of the study. Please note that individual feedback will not be possible.
I wish to receive feedback [ ]
Email: _____

(PRINT NAME)	
Signature of Participant:	Date:

Table F1

NPI total scores

ID	NPIATOT	NPIBTOT	NPICTOT	NPIDTOT	NPIETOT	NPIFTOT	NPIGTOT	NPIHTOT	NPIITOT	NPIJTOT	NPIKTOT	NPILTOT	NPITOTAL
1	0	0	0	0	2	0	0	0	0	0	0	0	2
2	0	0	0	0	0	1	0	0	2	0	0	0	3
3	2	6	6	4	12	0	8	0	0	0	0	0	38
4	0	0	12	0	0	0	0	0	0	0	8	0	20
5	0	0	0	0	2	0	6	0	0	0	0	0	8
6	0	0	1	0	1	0	0	0	0	0	1	0	3
7	1	0	0	3	0	0	9	1	0	1	4	0	19
8	0	8	1	1	2	0	1	0	0	0	0	0	13
9	0	0	0	1	0	0	1	0	0	0	0	0	2
10	1	0	2	1	1	0	1	1	0	4	0	0	11
11	1	0	0	4	1	0	0	0	0	0	0	0	6

Notes. The scores reported correspond to the total scores of each symptom, calculated as the product of severity (range 0-3) per frequency (range 0-4), and the total score overall, which is a sum of the total score of each symptom. *Abbreviations*. NPIA=delusions; NPIB=hallucinations; NPIC=agitation; NPID=depression; NPIE=anxiety; NPIF=elation/euphoria; NPIG=apathy; NPIH=disinhibition; NPII=irritability; NPIJ=aberrant motor behaviour; NPIK=sleep disorders; NPIL=appetite disorders.

Table F2

Overview of all participants recorded symptoms on the digital monitoring tool

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
	P1 - monitored from 07/02/2024 to 06/03/2024				
	Anxiety				
11/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	1	0	0
21/2/24	Has the person shown any other signs of anxiety?	2	1	1	2
22/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	2	1	1
24/2/24	Has the person shown any other signs of anxiety?	1	1	1	1
27/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	1	1	1
28/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	1	1	1
29/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	1	1	1
4/3/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	2	2	1	1
4/3/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	2	1	1
	P2 - monitored from 20/02/2024 to 17/03/2024				
	Euphoria				
20/2/24	Has the person appeared OR expressed feeling abnormally cheerful or happy, in a way that is different from their usual self?	1	2	0	1
20/2/24	Has the person shown an exaggerated self-confidence, different from their usual self?	1	2	0	1
24/2/24	Has the person appeared OR expressed feeling abnormally cheerful or happy, in a way that is different from their usual self?	1	1	1	0
24/2/24	Has the person found humour in and laughed at things that others do not find funny?	1	1	0	0
11/3/24	Has the person appeared OR expressed feeling abnormally cheerful or happy, in a way that is different from their usual self?	2	3	0	0

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
17/3/24	Has the person appeared OR expressed feeling abnormally cheerful or happy, in a way that is different from their usual self?	3	3	0	0
	Irritability				
20/2/24	Has the person shown OR expressed feeling rapid change of mood (for example: being fine one minute and irritable the next)?	1	2	0	1
20/2/24	Has the person shown signs of impatience (for example, having exaggerated trouble coping with delays, or waiting for planned activities)?	1	2	0	1
11/3/24	Has the person shown OR expressed feeling rapid change of mood (for example: being fine one minute and irritable the next)?	2	2	0	1
17/3/24	Has the person shown OR expressed feeling sudden flashes of anger?	2	1	0	3
	P3 - monitored from 04/02/2024 to 04/03/2024				
	Delusions				
4/2/24	Has the person shown any other type of paranoia/suspiciousness other than above?	3	1	1	2
11/2/24	Has the person shown any other type of paranoia/suspiciousness other than above?	3	1	1	2
11/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	2	1	0	2
12/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	3	1	1	2
16/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	2	1	0	0
18/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	2	1	0	0
20/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	2	2	0	1
4/3/24	Has the person shown any other unusual false beliefs that were not mentioned above?	3	1	1	1
	Hallucinations				
4/2/24	Has the person described hearing voices or sounds not heard by others, or acted as if hearing voices or sounds?	3	2	3	2
11/2/24	Has the person described hearing voices or sounds not heard by others, or acted as if hearing voices or sounds?	3	2	2	0
12/2/24	Has the person described hearing voices or sounds not heard by others, or acted as if hearing voices or sounds?	3	3	3	1

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
20/2/24	Has the person described hearing voices or sounds not heard by others, or acted as if hearing voices or sounds?	2	1	1	0
	Anxiety				
4/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	3	2	0	2
6/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	1	3
6/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	2	2	3
6/2/24	Has the person become nervous and upset when being separated from you?	2	1	1	1
9/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	2	2	0	1
9/2/24	Has the person reported having physical symptoms (for example, palpitations, shortness of breath, tightness in chest, dry mouth, dizziness), unexplained by any medical condition or ill health?	2	1	0	1
9/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	1	2
10/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	3	2	0	2
10/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	1	3
10/2/24	Has the person become nervous and upset when being separated from you?	3	1	1	2
11/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	3	2	1	3
11/2/24	Has the person reported having physical symptoms (for example, palpitations, shortness of breath, tightness in chest, dry mouth, dizziness), unexplained by any medical condition or ill health?	3	1	0	2
11/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	2	3
12/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	2	2	1	2
13/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	3	2	3
14/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	3	2	3
15/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	3	2	3

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
15/2/24	Has the person become nervous and upset when being separated from you?	2	1	0	2
16/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	1	2
18/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	2	0	1
20/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	1	2
20/2/24	Has the person reported having physical symptoms (for example, palpitations, shortness of breath, tightness in chest, dry mouth, dizziness), unexplained by any medical condition or ill health?	3	1	1	3
20/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	2	1	3
20/2/24	Has the person become nervous and upset when being separated from you?	3	1	1	2
24/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	3	1	2
25/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	2	2	1	2
25/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	3	1	2
26/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	3	1	2
27/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	2	1	2
1/3/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	3	2	2
2/3/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	3	1	3
3/3/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	2	2	2
4/3/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	2	1	2
	P4 - monitored from 14/02/2024 to 15/03/2024				
	Sleep				
18/2/24	Has the person slept excessively in the morning and had difficulty waking up?	2	1	2	2
24/2/24	Has the person slept excessively in the morning and had difficulty waking up?	2	1	1	2
24/2/24	Has the person shown any other types of irregular nighttime behaviours?	2	1	1	2

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
27/2/24	Has the person woken you up during the night?	2	1	1	0
27/2/24	Has the person slept excessively in the morning and had difficulty waking up?	2	1	1	2
28/2/24	Has the person woken you up during the night?	2	1	1	0
28/2/24	Has the person slept excessively in the morning and had difficulty waking up?	2	1	1	0
28/2/24	Has the person shown any other types of irregular nighttime behaviours?	2	1	1	0
8/3/24	Has the person woken you up during the night?	2	1	1	1
8/3/24	Has the person slept excessively in the morning and had difficulty waking up?	2	1	1	2
8/3/24	Has the person shown any other types of irregular nighttime behaviours?	2	1	1	1
13/3/24	Has the person woken you up during the night?	1	1	2	0
13/3/24	Has the person slept excessively in the morning and had difficulty waking up?	1	1	1	0
13/3/24	Has the person shown any other types of irregular nighttime behaviours?	2	1	2	0
	P5 - monitored from 17/02/2024 to 12/03/2024				
	Aberrant Motor Behaviour				
17/2/24	Has the person performed any repetitive movement? (for example: putting on/taking off clothes, handling buttons, wrapping strings)	1	3	2	0
21/2/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	2	1	0
22/2/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
23/2/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
26/2/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
27/2/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
1/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
3/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
4/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
7/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
10/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
11/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	0
12/3/24	Has the person shown signs of restlessness? (for example: fidgeting excessively, tapping fingers, bouncing feet, unable to sit still)	1	3	1	1
	P6 - monitored from 09/02/2024 to 08/03/2024				
	Anxiety				
12/2/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	1	2	1	1
12/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	2	1	1
	P7 - monitored from 14/02/2024 to 14/03/2024				
	Delusions				
22/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	1	1	1	0
24/2/24	Has the person shown any other unusual false beliefs that were not mentioned above? Had an important place to go	1	1	1	2
11/3/24	Has the person shown any other unusual false beliefs that were not mentioned above?	1	1	1	2
	Sleep				
17/2/24	Has the person woken you up during the night?	1	2	1	0

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
18/2/24	Has the person woken you up during the night?	1	2	1	1
19/2/24	Has the person woken you up during the night?	1	1	1	0
22/2/24	Has the person woken you up during the night?	2	1	1	0
22/2/24	Has the person woken up during the night and got dressed or planned to start the day (for example, by preparing breakfast, trying to go out) thinking it was already morning?	2	1	1	1
24/2/24	Has the person woken you up during the night?	2	2	1	1
24/2/24	Has the person woken up during the night and got dressed or planned to start the day (for example, by preparing breakfast, trying to go out) thinking it was already morning?	2	1	2	2
2/3/24	Has the person woken you up during the night?	1	2	1	0
4/3/24	Has the person woken you up during the night?	2	2	1	1
4/3/24	Has the person woken up during the night and got dressed or planned to start the day (for example, by preparing breakfast, trying to go out) thinking it was already morning?	2	1	2	1
5/3/24	Has the person woken you up during the night?	2	2	1	0
10/3/24	Has the person woken you up during the night?	1	2	1	0
	P8 - monitored from 15/02/2024 to 14/03/2024				
	Delusions				
16/2/24	Has the person shown any other unusual false beliefs that were not mentioned above?	3	1	2	2
	Hallucinations				
15/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	3	2	2	1
16/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	3	1	2	3
16/2/24	Has the person talked or communicated with people who are not there?	2	1	1	1
18/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	1	2	1
19/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	1	1	0

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
19/2/24	Has the person talked or communicated with people who are not there?	2	1	1	1
21/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	1	0	0
21/2/24	Has the person talked or communicated with people who are not there?	1	1	0	0
21/2/24	Has the person reported smelling an odour not smelled by others?	1	1	0	0
22/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	2	2	1	0
24/2/24	Has the person talked or communicated with people who are not there?	2	1	1	0
25/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	2	2	1	1
28/2/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	2	3	2	0
28/2/24	Has the person talked or communicated with people who are not there?	2	2	2	1
1/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	2	1	0
1/3/24	Has the person talked or communicated with people who are not there?	1	1	1	1
2/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	1	1	0
4/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	2	1	1	0
4/3/24	Has the person talked or communicated with people who are not there?	2	1	2	2
5/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	1	1	0
5/3/24	Has the person talked or communicated with people who are not there?	1	1	1	1
9/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	1	2	1	0
9/3/24	Has the person talked or communicated with people who are not there?	1	1	1	1
11/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	2	1	1	0
11/3/24	Has the person talked or communicated with people who are not there?	2	1	1	2
12/3/24	Has the person described seeing people or things that are not seen by other people and/or interacted with those?	3	2	2	0
12/3/24	Has the person talked or communicated with people who are not there?	2	2	2	2

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
	Anxiety				
16/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	3	1	2	3
16/2/24	Has the person shown any other signs of anxiety?	3	1	2	2
22/2/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	2	1	2	2
24/2/24	Has the person shown any other signs of anxiety?	1	1	2	2
25/2/24	Has the person shown any other signs of anxiety?	1	2	1	1
8/3/24	Has the person become nervous and upset when being separated from you?	1	2	1	1
9/3/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	2	1	2	2
9/3/24	Has the person become nervous and upset when being separated from you?	2	1	2	2
10/3/24	Has the person expressed feeling worried? (for example: about planned events, their physical or mental health, financial issues)	2	2	2	1
10/3/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	2	2	2
10/3/24	Has the person become nervous and upset when being separated from you?	2	1	1	2
	P10 - monitored from 23/04/2024 to 07/05/2024				
	Anxiety				
23/4/24	Has the person shown any other signs of anxiety?	1	1	1	0
25/4/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	1	1	1
30/4/24	Has the person shown physical signs of anxiety? (for example, trembling, being restless, being unable to relax)	1	1	2	2
	P11 - monitored from 26/03/2024 to 26/04/2024				
	Depression				
27/3/24	Has the person verbally expressed feeling sad or in low spirits and/or acted in a way that seems to indicate this? (for example: crying or sobbing)	2	1	2	1

Date	Subtype	Severity	Frequency	Caregiver Distress	Distress
27/3/24	Has the person shown disinterest in activities they would usually find enjoyable?	2	1	1	1
27/3/24	Has the person put themselves down or said they feel worthless?	2	1	1	1
27/3/24	Has the person appeared helpless, discouraged, or hopeless?	2	1	2	1
27/3/24	Has the person shown any other signs of depression?	2	2	2	1
28/3/24	Has the person verbally expressed feeling sad or in low spirits and/or acted in a way that seems to indicate this? (for example: crying or sobbing)	1	2	2	1
28/3/24	Has the person appeared helpless, discouraged, or hopeless?	1	2	2	1
30/3/24	Has the person verbally expressed feeling sad or in low spirits and/or acted in a way that seems to indicate this? (for example: crying or sobbing)	1	1	1	1
6/4/24	Has the person appeared helpless, discouraged, or hopeless?	1	1	0	1
7/4/24	Has the person verbally expressed feeling sad or in low spirits and/or acted in a way that seems to indicate this? (for example: crying or sobbing)	1	1	1	1
10/4/24	Has the person expressed a wish for death, or talked about killing themselves?	1	1	1	1
26/4/24	Has the person appeared helpless, discouraged, or hopeless?	1	1	1	2
10/5/24	Has the person expressed a wish for death, or talked about killing themselves?	1	1	1	1