

Neural Correlates of Delusions in Patients with Alzheimer's Disease

by

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Abstract

The neural correlates of delusions in Alzheimer's disease (AD) remain unclear. This thesis examined the neuropathological, structural volumetric, and resting-state functional connectivity (rs-fc) correlates associated with delusions in AD. We hypothesized that delusional AD patients will have greater disease severity characterized by higher AD pathology load and increased atrophy, as well as altered rs-fc compared to non-delusional patients. We found that delusions were associated with Lewy body pathology, vascular pathology, and vascular risk factors, but were not correlated with increased AD pathology. Patients who developed delusions showed increased atrophy of regions within the default mode network (DMN) following the onset of delusions, while the cohort that did not develop delusions did not exhibit significant atrophy in the DMN over a similar time frame. We found that decreased connectivity within the DMN, in particular disintegration of the inferior parietal lobule with the overall network, may be associated with delusions in AD.

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Statement of Contributions

Winnie Qian (author) solely prepared this thesis. All chapters, including the research plan, execution, analysis and writing were performed in whole or in part by the author. In part 1, Winnie carried out all data extraction and data analysis. In part 2, Winnie identified all the subjects from the NACC database, and conducted the VBM analyses with help from Nathan's imaging pipeline. In part 3, Winnie was the research assistant who recruited all study subjects and carried out the protocols of the study, including interviewing caregivers; running the PCA analysis using Nathan's pipeline; and conducting all statistical analyses.

Dr. Tom Schweizer (1) oversaw the development of the study protocol, participant testing, data analysis, and data interpretation of the current study, and (2) provided important feedback and detailed revisions of the thesis.

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Dr. Tarek Rajji assisted with the development of the study protocol, provided advice on project issues that arose, and provided important and detailed revisions of the thesis. Dr. Rajji also assisted with patient recruitment from the Centre for Addiction and Mental Health (CAMH) Memory clinic.

Dr. David Munoz assisted with the development of Chapter 3 and provided expertise on neuropathology of dementia.

Dr. Nathan Churchill trained me on how to use the PRONTO software that was used to analyze the fMRI data. He also trained me on the analysis of the VBM data and helped with any issues that came up during the analysis.

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List of Abbreviations

A β	Amyloid-beta
AD	Alzheimer's disease
AD+D	Alzheimer's disease patients with delusions
AD+DH	Alzheimer's disease patients with delusions and hallucinations
AD+H	Alzheimer's disease patients with hallucination
AD+P	Alzheimer's disease patients with psychosis
AD-P	Alzheimer's disease patients without psychosis
ADAS-Cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADC	Alzheimer's Disease Center
ADL	Activities of Daily Living
AFNI	Analysis of Functional Neuroimaging
a-MCI	Amnesic Mild Cognitive Impairment
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
ASL	Arterial Spin Labeling
BA	Brodmann area
BADL	Basic Activities of Daily Living
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease
BOLD	Blood Oxygen Level Dependency
BPRS	Brief Psychiatric Rating Scale

BPSD	Behavioral and Psychological Symptoms of Dementia
cAD	Clinically Diagnosed Alzheimer's Disease
cAD+D	Clinically Diagnosed Alzheimer's Disease Patients with Delusions
cAD+DH	Clinically Diagnosed Alzheimer's Disease Patients with Delusions and Hallucinations
cAD+H	Clinically Diagnosed Alzheimer's Disease Patients with Hallucinations
cAD+P	Clinically Diagnosed Alzheimer's Disease Patients with Psychosis
cAD-P	Clinically Diagnosed Alzheimer's Disease Patients without Psychosis
CDR	Clinical Dementia Rating
CEN	Central Executive Network
CERAD	Consortium to Establish a Registry of Alzheimer's Disease
CNS	Central Nervous System
CT	Computerized Tomography
DICOM	Digital Imaging and Communications in medicine
DLPFC	Dorsolateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of Mental-Disorders, version 4
FDA	Food and Drug Administration
FDG	Flurodeoxyglucose
GDP	Gross Domestic Product
GDS	Global Deterioration Scale
DAD	Disability Assessment for Dementia
DLB	Dementia with Lewy Bodies

DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
FA	Fractional Anisotropy
FAQ	Functional Activity Questionnaire
FDR	False Discovery Rate
FMRI	Functional Magnetic Resonance Imaging
FNIRS	Functional Near Infrared Spectroscopy
FSL	FMRIB Software Library
FEW	Family Wise Error
FWHM	Full-Width at Half Maximum
HPFB	Health Canada's Health Products and Food Branch
IADL	Instrumental Activities of Daily Living
ICA	Independent Component Analysis (ICA)
ICN	Intrinsic Connectivity Network
IPL	Inferior Parietal Lobe
MCI	Mild Cognitive Impairment
MEG	Magnetoencephalography
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MPFC	Medial Prefrontal Cortex

MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging
NACC	National Alzheimer’s Coordinating Center
NFT	Neurofibrillary Tangle
NIA-AA	National Institute on Aging and Alzheimer’s Association
NIFTI	Neuroimaging Informatics Technology Initiative
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association
NP	Neuropathology
npAD	Neuropathologically confirmed AD
npAD+	Neuropathologically confirmed AD with Delusions
npAD+DH	Neuropathologically confirmed AD with Delusions and Hallucinations
npAD+H	Neuropathologically confirmed AD with Hallucinations
npAD+P	Neuropathologically confirmed AD with Psychosis
npAD-P	Neuropathologically confirmed AD without Psychosis
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
OARS	Older Americans Resources and Services
PCA	Principal Component Analysis
PCC	Posterior Cingulate Cortex
PDD	Parkinson’s Disease Dementia
PET	Positron Emission Tomography

PFC	Prefrontal Cortex
PRONTO	PReprocessing Optimization Toolkit
ROI	Regions of Interest
REB	Research Ethics Board
RS-FMRI	Resting-State Functional Magnetic Resonance Imaging
RSN	Resting State Network
rTMS	Repetitive Transcranial Magnetic Stimulation
SAL	Subcortical Arteriosclerotic Leukoencephalopathy
SN	Salience Network
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SVD	Small Vessel Disease
TBS	Theta Burst Stimulation
TPJ	Temporoparietal Junction
UDS	Uniform Data Set
VBM	Voxel Based Morphometry
WMH	White Matter Hyperintensities

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Chapter 1:

Introduction

1.1. Background

1.1.1 Alzheimer's disease and diagnosis

It is estimated that 47.5 million people are living with dementia globally, and this figure is projected to triple by the year 2050 to 135.5 million (World Health Organization 2015). Each year there are 7.7 million new cases of dementia. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of all cases (Alzheimer's Association 2016). AD is a neurodegenerative disorder characterized by progressive cognitive decline in the domains of memory, language, and executive function that disrupt a person's basic activities of daily living (Wilson et al., 2012). These impairments are beyond those typical of normal aging. AD and related dementias incur a significant psychological, social, and economic burden to the patients, their families, and society. The global cost of dementia in 2010 was estimated to be US \$604 billion, which accounts for 1.0% of the global gross domestic product (GDP)(Alzheimer's Association 2016).

The criteria for dementia proposed by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) in 1984 has been shown to be a reliable assessment for the diagnosis of AD across multiple clinicopathological studies, at a sensitivity rate of 81% and specificity of 70% (Knopman et al., 2001; Schneider 2010). Physicians, often with the aid of neurologists, rely on a combination of tools to help make a diagnosis. The comprehensive evaluation includes obtaining medical and family history, including a psychiatric history

and the course of cognitive and behavioural changes, cognitive testing, neurological examinations, and blood test to rule out reversible causes. However, Nelson and colleagues reported that almost one in five patients diagnosed with dementia did not meet the pathological criteria for AD based on the NIA-Reagan guidelines (Nelson et al., 2010). Also, many scientists, especially those in clinical trials, advocated for a biomarker-based diagnostic criteria. Consequently, the NINCDS-ADRDA criteria were revised in 2011 with three key changes. The current diagnosis of AD is based on the criteria set by the National Institute of Aging and Alzheimer's Association (NIA-AA) working groups (McKhann et al., 2011). In contrast to the 1984 NINCDS-ADRDA guidelines, the NIA-AA guidelines 1) made the distinction between preclinical AD (Sperling et al., 2011), mild cognitive impairment (MCI) due to AD (Albert et al., 2011), and dementia due to AD (McKhann et al., 2011) rather than just one stage; 2) expanded the criteria so that memory impairments do not have to be the presenting or major symptom, recognizing that difficulties in word-finding and judgment may be a presenting symptom; and 3) included the potential of using biomarkers to estimate the likelihood of AD as the underlying cause of cognitive impairments. The NIA-AA criteria have been shown to have good predictive validity (Bouwman et al., 2010; Oksengard et al., 2010; Petersen et al., 2013; Prestia et al., 2013). However, there remains variability in diagnosis depending on the tools and approaches used during the clinical assessment, such as the neuropsychological tests and the biomarker assessments used. In addition, all the biomarkers being employed have considerable overlap with other dementias as well as non-demented elderly population. A recent analysis comparing the clinical and neuropathological data in 919 subjects from the National Alzheimer's Coordinating Center (NACC) found that the sensitivity of AD diagnosis ranged from 70.9-87.3%, while the specificity ranged from 44.3-70.8% (Beach et al., 2012). Therefore, autopsy diagnosis is still considered the gold standard for the confirmation of AD diagnosis. Despite established clinical guidelines, misdiagnosis of AD remains a concern, and, if possible, clinical trials and research studies should obtain neuropathological confirmation of AD rather than relying on a clinical diagnosis.

1.1.2 Psychosis in Alzheimer's disease

AD causes neurodegeneration of cortical structures that are responsible for cognition, emotion, and behaviour. Therefore it is unsurprising that, in addition to cognitive deficits, neuropsychiatric symptoms are highly prevalent in AD, affecting 42% of those in the mild stage, 80% in the moderate stage, and 90% in the advanced stage of AD (Mega et al., 1996). Neuropsychiatric symptoms can already be observed, although to a lesser extent, in the preclinical stages of AD. In MCI, a stage characterized by mild cognitive deficits (Petersen 2004), the prevalence of neuropsychiatric symptoms is estimated to affect 35-75% of patients (Van der Mussele et al., 2013).

Psychosis, consisting of either delusions or hallucinations, has been shown to be a valid and reliable symptom cluster (Cheng et al., 2012; Hollingworth et al., 2006; Kang et al., 2010), and is one of the most common phenomena to occur in AD. Delusions are defined as persistent false beliefs that are held despite evidence to the contrary. The context of delusions in AD are more in realm of possibility ("mundane") compared to the delusions typically seen in schizophrenia, which are more often "bizarre" beliefs (Berlyne 1972) of implausible events that likely never happened, such as the belief that one has been abducted by aliens. There are two main categories of delusions in AD (Cook et al., 2003; Reeves et al., 2012). Persecutory delusions is the more common type of delusion, with a prevalence of 7-40% in AD (Reeves et al., 2012) and making up 45-60% of delusions in dementia (Binetti et al., 1993; Webster & Grossberg 1998). Within persecutory delusions, delusion of theft is the most common (20-75% of persecutory delusions), followed by delusions of harm (10-30% of persecutory delusions), and delusions of jealousy and infidelity (2-16% of persecutory delusions) (Bassiony et al., 2000; Binetti et al., 1993; Cohen-Mansfield et al., 1998; Hwang et al., 1999; Ikeda et al., 2003; Leroi et al., 2003; Rao & Lyketsos 1998; Shinosaki et al., 2000). Persecutory delusions were described in the first index case of AD in 1907. Dr. Alois Alzheimer's first patient, Fran Auguste D., had delusions

of infidelity, excessive jealousy, and had believed her physicians were plotting to murder her (Alzheimer 1907). Although persecutory delusions are the most common, three-quarter of delusional patients exhibit more than one type of delusion (Migliorelli et al., 1995). The other main category of delusion is misidentification delusion, which makes up 25-47% of delusions in AD (Binetti et al., 1993; Burns et al., 1990; Forstl et al., 1994; Mendez et al., 1992). Misidentification delusions can include familiar persons (believing someone close to the individual is someone else; making up 16% of misidentification delusions), Capgras syndrome (thinking that someone is not who they say they are and is an imposter; making up 6-36% of misidentification delusions), phantom boarder (the belief that strangers are in the house; making up 20-30% of misidentification delusions), mirror delusion (misidentifies mirror images; 3% of misidentification delusions), nurturing syndrome (believing a dead family member is still alive), and thinking television images are real (5-7% of misidentification delusions). Misidentification can also extend to objects, such as the belief that the house is not one's home (9-18% of misidentification delusions) (Ballard & Walker 1999; Cohen-Mansfield et al., 1998; Harwood et al., 1999; Hwang et al., 2003; Ikeda et al., 2003; Leroi et al., 2003; Mendez et al., 1992; Schlimme et al., 2002; Shinosaki et al., 2000). Persecutory delusions are usually found earlier in the disease course than misidentification delusions, and, as such, are believed to require a greater level of preserved cognition (Bassiony & Lyketsos 2003). The majority of studies found that the cognitive level, as measured by MMSE, is comparable between persecutory delusional patients and AD patients without delusions (Hwang et al., 1999; Hwang et al., 1997; Shinosaki et al., 2000; Targum & Abbott 1999; Tsai et al., 1997). Meanwhile, patients with misidentification delusions show lower MMSE scores than matched non-delusional patients (Forstl et al., 1994). Hallucinations are defined as experiencing perceptions in the absence of external stimuli, and can be in the form of auditory, visual, tactile, olfactory, or gustation. In AD, hallucinations are usually in the form of visual or auditory, with visual hallucinations being more common (Jeste & Finkel 2000; Rubin et al., 1988; Tariot et al., 1995). This is in contrast to schizophrenia where auditory hallucinations are more common (Bassiony & Lyketsos 2003).

1.1.3 Epidemiology of psychosis

1.1.3.1 Prevalence

In one of the largest studies to date, Ropacki and Jeste reviewed 55 studies, which included 9749 subjects, and found that the mean prevalence of psychosis in AD is 41.1%, ranging from 12.2% to 74.1% (Ropacki & Jeste 2005). Psychosis in AD is the second most prevalent psychotic disorder, after schizophrenia, with the trend to surpass that of schizophrenia in upcoming years (Murray et al., 2014b). Delusion is the more common type of psychosis with a median prevalence rate of 36% (range of 9.3%-63%) (Bassiony et al., 2000; Flint 1991; Paulsen et al., 2000b; Ropacki & Jeste 2005; Sultzer et al., 1992; Wragg & Jeste 1989), while hallucinations are less common at a median prevalence of 18% (range of 4%-41%) (Lyketsos et al., 2000; Mega et al., 1996; Paulsen et al., 2000b; Ropacki & Jeste 2005; Sultzer et al., 1992). It's estimated that 13% (range of 7.8-20.8%) of AD patients experience both delusions and hallucinations, although not necessarily concurrently. These prevalence rates are likely underestimations, as some studies consider subjects with misidentifications, reported in 3.6%-38.9% of cases, as a distinct phenomenon separate from delusions or hallucinations (Ropacki & Jeste 2005). On the other hand, the lack of clarity in the definition of psychosis, especially delusions, may result in other phenomena such as confabulations to be lumped in with delusions, thereby inflating the prevalence.

The prevalence of psychosis in AD varies widely, and may be attributable to the sample source, the dementia stage, and the definition of psychosis. Psychosis is more prevalent in inpatient settings (psychosis prevalence of 31.2%-74.1%; delusional prevalence of 44.4%-62.9%; hallucination prevalence of 5.4%-34%) compared to outpatient memory or research clinics (psychosis prevalence 12.2%-65.2%; delusional prevalence of 9.3%-63%; psychosis prevalence of 3.8%-41%) (Ropacki & Jeste 2005). The prevalence of psychosis may also be dependent on the dementia stage. Psychosis appears to be more prevalent in

the later stages of dementia compared to the earlier and prodromal stages (Drevets & Rubin 1989; Sweet et al., 2010b).

1.1.3.2 Assessment tools for psychosis

Different psychometric scales have been utilized to measure behavioural symptoms, including structural clinical interview according to the Diagnostic and Statistical Manual of Mental-Disorders (DSM-IV); the Neuropsychiatric Inventory (NPI); the Brief Psychiatric Rating Scale (BPRS); the Cohen-Mansfield Agitation Inventory; the Clinical Global Impression of Change; the Clinical Global Impression of Severity; and the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD). The most widely used assessment tool for neuropsychiatric symptoms in AD is the NPI (Cummings et al., 1994), which has different versions including a shorter questionnaire version, the NPI-Q (Kaufer et al., 1998). The NPI is a validated behavioural symptom scale that rates the frequency, severity, and caregiver distress on 12 neuropsychiatric symptom domains, including delusion, hallucination, agitation/aggression, depression, anxiety, elation, apathy, disinhibition, irritability, and aberrant motor behaviour. The NPI-Q, including each of the subscales independently, is validated in the dementia population, and has the advantage of being brief and not requiring any clinical evaluation (Trzepacz et al., 2013). The NPI and NPI-Q have been shown to have adequate test-retest validity and interrater reliability, and good concurrent validity compared to the BEHAVE-AD, Hamilton Depression Rating Scale, and the Brief Psychiatric Rating Scale (BPRS) (Kaufer et al., 1998). The NPI-Q has adequate convergent validity both with total and individual symptom domains and caregiver distress rating on the NPI (Kaufer et al., 1998). The NPI-Q is consistent with the NPI with only a 5% false-positive rate on the shorter version (Kaufer et al., 1998). The NPI-Q also has been shown to have good convergent validity with regional atrophy on magnetic resonance imaging (MRI), regional hypometabolism on flurodeoxyglucose (FDG) position emission tomography

(PET), regional hypoperfusion on single photon emission computed tomography (SPECT), and autopsy studies of plaques, tangles, and neurochemical parameters (Cummings 1997).

1.1.3.3 Incidence

Weamer et al. investigated the incidence of psychosis in 776 elderly subjects with mild cognitive impairment or AD (Weamer et al., 2016). Their reported annual incidence of psychosis was 11.7% in AD (9-14%), which was relatively stable over time, with a 3-year cumulative incidence rate of 35% (31-39%) and 5-year cumulative incidence rate of 52% (47-57%). The incidence of psychosis in mild cognitive impairment was significantly lower, at a 3-year cumulative incidence of 4% (1-11%) and 5-year cumulative incidence of 12%. Weamer and colleagues also stratified the risk by the severity of cognitive impairment, and found that psychosis incidence was strongly associated with cognitive status. Moderate to severe AD patients (MMSE of 0-19) had an annual incidence of 20%, 3-year cumulative incidence of 48%, and 5-year incidence of 61%, compared to mild AD patients (MMSE 20-24) who had an annual incidence of 8%, 3-year cumulative incidence of 33%, and 5-year incidence of 48%. Overall, it appears that the frequency of delusions increases as AD first progresses, but the frequency decreases as the disease becomes more severe. Meanwhile, hallucinations appear to be relatively rare in the early stages of AD, but increase in frequency as the disease progresses (Bassiony & Lyketsos 2003; Devanand et al., 1992; Jost & Grossberg 1996).

1.1.3.4 Persistence

The persistence, referring to the symptom being present at consecutive time points, of psychotic symptoms over time is unclear, as different studies have different follow-up periods. On the higher end of the spectrum, Rosen et al. and Zubenko et al. found that the

persistence of psychotic symptoms annually was 86.7% and 84.6%, respectively (Rosen & Zubenko 1991; Zubenko et al., 1991). Levy et al. found that 57% of subjects continued to exhibit psychosis on at least two consecutive evaluations, each spaced 3 months apart (Levy et al., 1996). Vilalta-Franch et al., who evaluated participants every six months for two years found that psychotic symptoms persisted in 68.7% of cases after one year (Vilalta-Franch et al., 2013). Burns et al. found that, after one year, the persistence of delusions was 44%, visual hallucination was 26%, and auditory hallucination was 45% (Burns et al., 1990). In contrast, Haupt et al. found that none of the 32 subjects who exhibited psychosis at baseline (21 delusional and 11 hallucinatory subjects) showed psychosis after 2 years (Haupt et al., 2000). Similarly, Devanand et al. found low persistence rates of 12.8% for delusions and 5.6% for hallucinations after 2 years (Devanand et al., 1997). However in the majority of the studies, the use of antipsychotic or cholinesterase inhibitors were not exclusion factors so the persistence rates reported may not have reflected true values.

1.1.4 Clinical correlates of psychosis

Psychotic patients have been identified as a subgroup within AD that is associated with more adverse outcomes (Murray et al., 2014b; Vilalta-Franch et al., 2013). Compared to patients without psychosis, patients who develop psychosis have been found to have greater cognitive impairment (Levy et al., 1996; Ropacki & Jeste 2005); an earlier age of AD onset (D'Onofrio et al., 2016); a faster rate of cognitive (Emanuel et al., 2011; Koppel et al., 2012; Levy et al., 1996; Peters et al., 2015; Ropacki & Jeste 2005; Seltman et al., 2016) and functional decline (D'Onofrio et al., 2016; Scarmeas et al., 2005); higher rate of other neurobehavioural symptoms such as depression (D'Onofrio et al., 2016; Lyketsos et al., 2001), agitation (Bruen et al., 2008; D'Onofrio et al., 2016; Gilley et al., 1991), and aggression (Aarsland et al., 1996; D'Onofrio et al., 2016; Deutsch et al., 1991; Doody et al., 1995; Forstl et al., 1993a; Gilley et al., 1997; Kotrla et al., 1995a; Sweet et al., 2001); poorer

overall health (Bassiony et al., 2000); increased rates of institutionization into nursing homes (Scarmeas et al., 2005; Steele et al., 1990); and higher rates of mortality (Vilalta-Franch et al., 2013; Wilson et al., 2006). Unsurprisingly, caregivers to AD patients with psychosis experience and report higher rates of caregiver burden and distress (Fischer et al., 2012b; Gauthier et al., 2010; Kaufer et al., 1998). Although most studies utilized global measures of cognition, studies that looked at individual domains of cognition found greater frontal deficits, particularly in working memory, in association with psychosis (Jeste et al., 1992; Koppel et al., 2012; Koppel et al., 2014c; Paulsen et al., 2000a; Paulsen et al., 2000b).

1.1.6 Genetics of psychosis

The strongest genetic risk factor for late onset Alzheimer's disease is the Apolipoprotein E (APOE) gene, which has three common allelic forms: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 2$ allele, which is rare in the population, appears to be protective (Nagy et al., 1995), while inheritance of the $\epsilon 4$ allele significantly increases the risk of Alzheimer's in a dose-dependent manner (Farlow 1997; Farrer et al., 1997). One copy of the $\epsilon 4$ allele is estimated to triple the likelihood of AD while two copies increase the likelihood by 15 times (Farrer et al., 1997). The $\epsilon 4$ allele is believed to increase the neuropathological hallmarks of AD by interfering with A β clearance as well as contributing to neurodegeneration (Bu 2009; Castellano et al., 2011).

Psychosis in AD has an established genetic component of 30-60% (Bacanú et al., 2005; Sweet et al., 2002b). The impact of the *APOE* $\epsilon 4$ allele on the risk of AD has prompted several studies to consider the *APOE* gene as a candidate gene for psychosis. However, the results have been conflicting, with some studies reporting a positive association (Ballard et al., 1997; Harwood et al., 1999; Kim et al., 2017; Ramachandran et al., 1996; Scarmeas et al., 2002; Weiner et al., 1999; Zdanys et al., 2007) while the majority did not find any

association (Cacabelos et al., 1997; Cantillon et al., 1997; DeMichele-Sweet & Sweet 2010; Forsell et al., 1997; Gabryelewicz et al., 2002; Hirono et al., 1998b; Lehtovirta et al., 1996; Levy et al., 1999; Lopez et al., 1997; Lyketsos et al., 1997; Panza et al., 2012; Schmand et al., 1998; Sweet et al., 2002a). Furthermore, *APOE* genotype may affect the sexes differently. Kim et al. recently found that the *APOE* $\epsilon 4$ allele increases the risk of psychosis only in females (Kim et al., 2017). Thus, a consensus has yet to be reached regarding the effect of *APOE* $\epsilon 4$ on the risk of psychosis.

Other genes that have been proposed to be associated with psychosis include genes that code for serotonin and dopamine receptors, as well as for the catechol-O-methyltransferase enzyme (DeMichele-Sweet & Sweet 2010). However, the association between these genes and psychosis remain inconclusive.

1.1.7 Delusions versus hallucinations

It is now recognized that psychosis in AD represents a distinct endophenotype of AD (DeMichele-Sweet & Sweet 2010). There is further substantial evidence to suggest that delusions and hallucinations have different etiologies, clinical correlates and trajectories, lending support that they should be considered separately (Fischer & Sweet 2016).

Previous studies, especially genetic, neuropathological, and epidemiological, typically combined delusions and hallucinations under a broad category of psychosis (Bassiony & Lyketsos 2003). Although there are benefits to this approach, including a larger sample size and ease of classification given the high co-morbidity of these symptoms, there are evidence mounting from clinical and neuroimaging studies showing that they are distinct entities (Fischer & Sweet 2016). For instance, hallucinations have been found to manifest later in the disease course and have been found to be associated with more severe

cognitive deficits than delusions (Burns et al., 1990). There are also differences in clinical risk-factor associates between the symptoms (Bassiony et al., 2000). Male gender appears to be a risk factor for delusions but not hallucinations (Burns et al., 1990), while other factors such as lower education, African-American race, and greater cognitive severity only appear to be risk factors for hallucinations (Bassiony et al., 2000).

Therefore combining delusions and hallucinations can obscure important differences between them. Delusions and hallucinations may reflect separate subphenotypes with different underlying mechanisms. However, disentangling them may be challenging, given that they often co-exist, or manifest during different times over the disease course.

1.1.8 Treatment

Despite the high prevalence of AD and the substantial efforts to find a cure, current treatments are only marginally effective. Furthermore, the current treatment approaches for psychosis in AD have poor efficacy. The first-line pharmacotherapy used to treat psychosis in AD are atypical antipsychotic (aripiprazole, quetiapine, olanzapine, risperidone) (Canadian Coalition for Seniors Mental Health (CCSMH) 2006), which were first developed and approved for the management of psychosis in patients with schizophrenia (Ballard et al., 2011; Foster et al., 2016b; Gardner et al., 2005). Results from meta-analyses have shown that the use of atypical antipsychotics in AD is somewhat beneficial in placebo-controlled trials, and have fewer side effects than conventional antipsychotics, such as Parkinsonism, tardive dyskinesia, and akathisia (Ballard et al., 2011). However, the effects are mediocre at best and are inconsistent (Koppel & Greenwald 2014). Furthermore, large-scale meta-analyses have found that atypical antipsychotics increase the risk of mortality in AD by 1.5-1.7 times (Herrmann & Lanctot 2005; Herrmann & Lanctot 2006; Schneider et al., 2005; Trifiro et al., 2009). Consequently, Health Canada's

Health Products and Food Branch (HPFB) and the US Food and Drug Administration (FDA) have included “black-box” warnings for atypical anti-psychotics (Health Canada 2005; Schneider et al., 2005; Valiyeva et al., 2008). In addition to increased risk of mortality, the drugs are associated with significant morbidity, including an increased risk of cerebrovascular events, extrapyramidal motor symptoms, greater cognitive decline, infections, and falls (Herrmann & Lanctot 2005; Herrmann & Lanctot 2006; Schneider et al., 2005). In a later study, Schneeweiss et al. found that conventional antipsychotics, which do not carry the black-box warning, were comparable, or perhaps worse, than atypical antipsychotics (Schneeweiss et al., 2007). Therefore there is a great need to better understand the pathophysiology of psychotic symptoms in AD in order to generate novel treatment strategies that are specifically tailored for AD, rather than relying on treatments designed for other patient populations.

1.2 Neuropathology

1.2.1 Neuropathology of AD

The pathology of AD is characterized by the accumulation of two abnormally folded proteins: amyloid-beta ($A\beta$) proteins that aggregate to form plaques, and tau proteins that which form neurofibrillary tangles (Arriagada et al., 1992). These misfolded proteins, $A\beta$ especially, are believed to be toxic to nerve cells and trigger the neurodegenerative process (Boyle et al., 2013; Karran et al., 2011). The tau pathology has generally been believed to be downstream of $A\beta$ pathology, but it is possible they can occur independently with summative effects (Small & Duff 2008). While the amyloid hypothesis has been posited more than three decades ago, the cause of these pathological abnormalities remains a mystery.

Several neuropathological criteria have been established to quantify AD pathology post-mortem. The Consortium to Establish a Registry of Alzheimer's Disease (CERAD) is a method for rating the extent of amyloid plaque, categorized as sparse, moderate, or frequent (Mirra et al., 1991). The Braak and Braak staging has been used to quantify the extension of neurofibrillary tangle pathology progression (Braak & Braak 1991). Braak posited that the accumulation of neurofibrillary tangles follows a specific pattern in the brain, starting in the entorhinal/transentorhinal cortex, spreading to the hippocampi and mesiotemporal areas, and then finally to the isocortical association regions (Braak & Braak 1991). Individuals in stages I and II are usually asymptomatic; those in stages III and IV are incipient AD; and those in stages V and VI are usually symptomatic. The NIA-Reagan Institute neuropathological criteria, established in 1997, integrated the CERAD and Braak staging to estimate the likelihood of dementia being due to AD as either high, intermediate, low, or not met (1997) (Figure 3.2).

1.2.1 Neuropathology of Psychosis

Investigations into the neuropathology of psychosis have produced conflicting results, with several studies showing increased AD pathology load with psychosis while others did not find any significant association. Zubenko et al. investigated the amount of senile plaques and neurofibrillary tangles in a sample of 13 AD patients with psychosis and 14 without psychosis and found higher senile plaque density in the prosubiculum as well as higher neurofibrillary tangle density in the middle frontal cortex of psychotic patients (Zubenko et al., 1991). Farber and colleagues followed 109 AD patients until death and found that patients who developed psychotic symptoms (63% of the sample) had over twice the density of neurofibrillary tangles in their neocortex compared to patients without psychosis, independent of dementia severity (Farber et al., 2000). Farber and colleagues however did not find any association between psychosis and plaques density. Murray and colleagues found that AD patients with psychosis (n=19) had significantly more

phosphorylated tau in the prefrontal cortex compared to non-psychotic AD controls (n=26) (Murray et al., 2014a). Koppel and colleagues found significantly higher levels of phosphorylated tau in the prefrontal cortex of psychotic AD patients (n=45) compared to non-psychotic patients (n=26), but only in female patients (Koppel et al., 2014a). Meanwhile male psychotic patients had greater alpha-synuclein pathology, which makes up Lewy bodies and is considered a pathological hallmark of Parkinson's disease. Koppel and colleagues, in a separate study, also found increased tau in the cerebrospinal fluids of psychotic AD patients (n=60) compared to non-psychotic patients (n=115)(Koppel et al., 2013). The findings of positive association between AD pathology load and psychosis seems to indicate that psychosis represents a more severe form of AD.

On the other hand, Sweet and colleagues compared the brains of 24 AD patients with psychosis to 25 AD patients without psychosis and did not find increased plaques or neurofibrillary tangles in the psychotic group, after controlling for Lewy body pathology (Sweet et al., 2000). Skogseth and colleagues similarly did not find any association between psychosis and tau nor beta-amyloid in the cerebrospinal fluid of 32 AD patients, although in this sample only 4 patients had delusional symptoms and it is unclear how many patients had hallucinations (Skogseth et al., 2008). In addition, Jacobson and colleagues found that plaque and tangle densities were associated with visual hallucinations in patients with a clinicopathological diagnosis of Parkinson's disease, but not in AD (Jacobson et al., 2014). As such, if patients with Parkinson's disease were clinically misdiagnosed with AD and included in studies, it may lead to the false conclusion that plaques and tangles are associated with hallucinations. These studies suggest that psychotic symptoms may be mediated by an alternate mechanism that is independent, or progresses in parallel, with AD pathology.

Lewy body is a core pathological feature of dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), two disorders where psychosis is extremely prevalent

(Jacobson et al., 2014). Hallucinations are estimated to occur in 76% of patients with DLB and in 54% of patients with PDD, while delusions are estimated to occur in 57% of patients with DLB and 29% of patients with PDD (Jacobson et al., 2014). Given that Lewy body pathology co-occur with AD pathology 50% of the time (Hamilton 2000), they may have a mediating effect in AD as well. Current evidence has indicated that visual hallucinations are more common in patients with primary AD plus comorbid Lewy body pathology, but other forms of hallucinations and delusions are not more common (Ballard et al., 2004; Tsuang et al., 2006). In addition, 40% to 60% of AD patients without Lewy body pathology have psychosis (delusions and/or auditory and visual hallucinations) (Tsuang et al., 2006). Therefore, Lewy bodies are neither necessarily nor sufficient to produce psychotic symptoms.

There has only been one study that investigated vascular pathology and psychosis in AD, which was published after the neuropathology section of the current thesis. Ting and colleagues assessed vascular pathology in 145 patients with confirmed AD, including 50 with psychosis, from the National Alzheimer's Coordinating Center (NACC) database (Ting et al., 2016). The authors found that the presence of microinfarcts and moderate to severe arteriosclerosis were positively associated with psychosis. However, this study did not assess delusions and hallucinations separately.

Overall, the neuropathological correlates of psychosis in AD are unclear. Previous evidence suggests that AD pathology, Lewy body pathology, and vascular pathology may all play a role. The variability of previous studies could be due combining delusions and hallucinations as a single psychosis entity; examining different brain regions of interest; small sample sizes; not accounting for comorbid Lewy body or vascular pathology; and relying on a clinical, rather than pathological, diagnosis of AD.

1.3 Neuroimaging Methods

A variety of neuroimaging modalities are used to scan for both the structure and function of the central nervous system. Structural techniques, including magnetic resonance imaging (MRI), computerized tomography (CT), and diffusion tensor imaging (DTI) are used to visualize grey matter volume, white matter hyperintensities (WMH), ventricle sizes, and other physical features of the brain. Functional techniques, including positron emission tomography (PET) and SPECT, are used to measure parameters of brain function such as cerebral blood flow and glucose metabolism (Cai et al., 2016; Foster et al., 2016a; Hays et al., 2016; Jack & Holtzman 2013; Li et al., 2016). Functional imaging can be used to visual brain activity at rest or when it is active in response to an external task or stimuli.

Neuroimaging has been widely used for both clinical and research purposes. In the clinical assessment of dementia, both structural and functional imaging are used in conjunction with neurological examinations, neuropsychological assessments, and clinical interviews to aid in the diagnosis. CT or MRI is often used to assess for the presence of any atrophy, cerebrovascular disease, tumors, or inflammation. One of the earliest structural brain markers of AD that can already be detected in patients with MCI include atrophy of the medial temporal lobes, particularly the hippocampus and entorhinal cortex (Ferreira et al., 2011). Other areas that are vulnerable to atrophy in AD include the posterior cingulate gyrus, precuneus, splenium of the corpus callosum on the medial surface, the posterior parietal lobe, superior temporal, and frontal regions (Joko et al., 2016; Kilimann et al., 2014; Krumm et al., 2016; Thompson et al., 2001; Wirth et al., 2013). SPECT or PET is often used in combination with structural imaging to assist in differential diagnosis. It is recognized that different forms of dementia have different patterns of cerebral blood flow and metabolism (Kato et al., 2016). Functional brain markers of AD include decreased perfusion to the frontal, temporal, and parietal regions (Frings et al., 2015; Herholz 2011; Moretti 2015). In addition, PET can be used to visualize A β and tau, although tau-PET has

not yet been approved for clinical use.

In the research setting, imaging techniques including voxel-based morphometry, DTI and functional MRI are becoming increasingly used to elucidate the structural and functional hallmarks of neuropsychiatric disorders; to measure disease progression and treatment efficacy; to detect early pre-symptomatic changes; and to identify the neural correlates and novel biomarkers of a disease.

1.3.1 Voxel-based morphometry

Voxel-based morphometry (VBM) is an imaging analysis technique for the characterization of grey and white matter differences on MRI. VBM works by measuring tissue concentration at each voxel of the brain, and then statistically comparing them between two groups. The VBM approach has been widely used in the AD population.

1.3.2 fMRI and Blood Oxygen Level Dependency (BOLD) signal

Functional MRI (fMRI) is a functional neuroimaging technique that measures brain activity based on indirect markers of brain activation. fMRI relies on blood oxygenation level dependent (BOLD) signal intensity changes in the brain tissues to infer brain activity, which is derived from a combination of oxygenation, blood flow, and blood volume (Ogawa et al., 1992). The BOLD signal utilizes the difference between the magnetic properties of oxygenated hemoglobin, which is diamagnetic, and deoxygenated hemoglobin, which is paramagnetic (Ogawa et al., 1992). A brain area that is active would presumably have greater oxygen and blood supply demands, causing a temporary increase in regional oxygen consumption. fMRI can measure brain activity in response to a task (task-based

fMRI), or at rest (resting-state fMRI, rs-fMRI). Activation is when the BOLD signal is higher during the experimental task compared to rest or controls, while deactivation is when the BOLD signal is higher during rest or in controls than during experimental tasks.

1.3.3 Resting-state fMRI

Our initial understanding of brain anatomy and cognition was based on the modular paradigm, the thought that individual brain regions independently give rise to specific cognitive functions (Downing et al., 2001; Kanwisher et al., 1997). However, there is a growing body of literature suggesting that the modular paradigm is limited and does not accurately describe how complex cognitive functions are formed (Fuster 2000). The current school of thought is moving towards analyzing large-scale brain networks that involve a host of different regions working in synchrony to mediate cognitive functions. A specific brain area can then be considered as part of a large-scale network, although the function of each unitary area is still being considered to help elucidate the function of the overall network.

Rs-fMRI is a novel technique that measures the baseline spontaneous activity of the brain when a person is “resting”, i.e. not actively engaging in any externally cued tasks. Rs-fMRI has been used to identify various functional resting-state networks (RSNs) (Biswal et al., 2010; Ogoh & Ainslie 2009; Shehzad et al., 2009). These networks comprise of spatially distinct brain regions whose spontaneous low-frequency BOLD fluctuations (<0.1 Hz) are temporally correlated (Fox & Raichle 2007). The assumption is that if two regions have a highly correlated BOLD activity, they are connected and are communicating with each other (Biswal et al., 1995; Damoiseaux et al., 2006; Greicius et al., 2003). These patterns of intrinsic neural activities are basic properties in healthy brains, and have been shown to play an important role in cognitive functions. Using graph theory, it has been shown that

network connectivity is directly related to the efficiency in the ability to integrate and communicate information (Achard & Bullmore 2007; Bullmore & Sporns 2009; Buzsaki & Draguhn 2004; Chen et al., 2006a; Grigorov 2005; Latora & Marchiori 2001; Mathias & Gopal 2001). Empirical studies have further supported this by showing that resting-state network connectivity of the dorsolateral prefrontal cortex was predictive of intellectual performance (Song et al., 2008), and that the robustness of network connectivity was correlated with IQ scores (van den Heuvel et al., 2009). Taken together, these studies suggest that resting-state networks facilitate information processing and integration. It is therefore unsurprising that resting-state activity consumes about 60-80% of the brain's energy (Fox & Raichle 2007). Rs-fMRI has also proven to have important clinical value, as evidence has shown that alterations in particular RSNs are implicated in a variety of neuropsychiatric disorders (Filippini et al., 2009; Greicius et al., 2004). Functional connectivity between regions does not necessarily have to be anatomically connected, even though anatomically connected regions usually show high functional connectivity (Greicius et al., 2004). It is also important to note that these alterations in functional connectivity merely indicate deviation from the norm, and increases or decreases do not necessarily correlate with brain region activation for tasks.

1.3.3.2 Core functional networks

Several functional brain networks have been identified to date (Lee et al., 2013b). Converging evidence suggests that dysfunctions in specific core functional networks may mediate the transition from neuropathology to clinical, cognitive symptoms (Cordova-Palomera et al., 2016; Jones et al., 2016). According to the triple network model of pathology (Menon 2011), three networks—the default mode network, salience network, and central executive network—have been identified as core networks playing a crucial role in the development of many neuropsychiatric disorders (Menon 2011; Palaniyappan & Liddle 2012). Altered connectivity and altered anti-correlation in these networks have

been implicated in AD (Buckner et al., 2008), schizophrenia (Bressler 2003; Ford & Mathalon 2008), major depression (Buckner et al., 2008), the manic phase of bipolar (Bhattacharya 2001), autism (Murias et al., 2007; Uhlhaas & Singer 2007; Welsh et al., 2005), Parkinson's disease (Timmermann et al., 2003), and in normal aging (Grady et al., 2006). Therefore, functional network changes may represent a parsimonious account for a common pathophysiology of neuropsychiatric disorders.

Default mode network (DMN): The DMN has been the most extensively investigated RSN, and have been shown to be vulnerable in several patient populations. Perhaps due to the high metabolic requirements of the DMN, it is particularly vulnerable to atrophy and functional alterations in the presence of A β deposits (Greicius et al., 2004; Minoshima et al., 1997; Sheline et al., 2010; Sperling et al., 2010; Sperling et al., 2009). The DMN shows greater activity when the brain is in its passive state, and “deactivates” during cognitive tasks. The DMN is therefore described as “task-negative” and is temporally anti-correlated with task-positive networks. The exact function of DMN is difficult to discern, but it is presumably activated when someone is engaged in internally focused tasks such as self-monitoring, thinking about the self and others, autobiographical memory retrieval, mind-wandering, and envisioning the future (Buckner et al., 2008; Cabeza et al., 2002; Fair et al., 2008; Greicius et al., 2004; Gusnard et al., 2001; Leech et al., 2011; Mason et al., 2007). The DMN is anchored in the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC), and inferior parietal lobes (IPL)(Greicius et al., 2004; Gusnard et al., 2001). In addition to these core regions, the DMN may also consist of hippocampus and adjacent regions in the medial and lateral temporal lobe, as well as the temporoparietal junction (TPJ) (Andrews-Hanna et al., 2010; Buckner et al., 2008; Shulman et al., 1997). The precuneus and PCC are key nodes both within the DMN and as key points of contact between DMN and other networks, making them network “hubs” (Fransson & Marrelec 2008; Gusnard et al., 2001). It has been suggested that the DMN can be further subdivided into three sub-networks: a ventral component consisting of the retrosplenial cortex and medial temporal cortex; a dorsal component consisting of anterior prefrontal regions; and

a posterior component consisting of parietal regions (Damoiseaux et al., 2012). These sub-networks of the DMN may be related to different cognitive processes: ventral DMN/medial temporal lobe may be related to creating mental images based on memory; anterior DMN may be related to self-referential processes; and posterior DMN may be related to autobiographical memory (Qin et al., 2012; Uddin et al., 2009; Whitfield-Gabrieli et al., 2011). The sub-networks have been found to progress differently through the disease course (Andrews-Hanna et al., 2010; Leech et al., 2011; Qin et al., 2012; Uddin et al., 2009; Whitfield-Gabrieli et al., 2011). For instance, posterior DMN connectivity has been shown to be reduced earlier in the AD disease progression than anterior and ventral DMN (Damoiseaux et al., 2012). However, the sub-networks are not always generated separately in resting-state analyses.

Central executive network (CEN): The CEN, also termed the fronto-parietal network, is another core cognitive network, responsible for high-level cognitive functions such as attention, response selection, and working memory. Given the involvement in these cognitive functions, the CEN is typically activated during task-positive tasks. Key nodes of this network are the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) (Seeley et al., 2007).

Salience network (SN): The SN is the third core cognitive network, and is involved in monitoring and integrating salient external events with internal events (Seeley et al., 2007; Uddin et al., 2011). Recent studies have indicated that the SN is responsible for the dynamic switching between DMN and CEN activation, which are anti-correlated (Uddin et al., 2011). These two networks show competition, where DMN is involved in internally oriented thoughts while the CEN is involved in externally oriented thoughts (Sridharan et al., 2008). Key nodes of the SN include the anterior cingulate cortex and the bilateral anterior insula (Uddin et al., 2011). Additional regions that are proposed to be part of the SN include

temporal lobe (superior and middle temporal gyri), frontal gyrus (middle and inferior frontal gyri), and limbic system structures (Garcia-Garcia et al., 2013; White et al., 2010).

1.3.4 Strength of MRI versus other neuroimaging techniques

Many imaging techniques have emerged to visualize the structure and function of the brain, each with their own strengths and limitations. When choosing a modality, several features are taken into consideration, including spatial resolution, temporal resolution, cost, invasiveness to the subject/patient, and practicality in testing the research question.

Amongst the modalities, (f)MRI is superior in many regards for both structural and functional imaging. Compared to other structural techniques such as CT, MRI has higher spatial resolution (Lev & Grant 2000) for accurately localizing the anatomical structure, higher contrast, and does not emit any radiation (Crosson et al., 2010; Lev & Grant 2000).

Compared to other functional modalities, fMRI has better temporal resolution than PET (in the range of tens of seconds compared to seconds) (Crosson et al., 2010). Although electroencephalography (EEG) and magnetoencephalography (MEG) have better temporal resolution than fMRI, it is at the expense of far worse spatial resolution. FMRI strikes a better balance between temporal and spatial resolutions (Crosson et al., 2010). In addition, fMRI can visualize deeper brain structures such as the thalamus, hypothalamus, amygdala, and cerebellum, whereas other techniques (e.g. functional Near Infrared Spectroscopy, (fNIRS), EEG, MEG) can only detect surface level activity. These subcortical brain regions are highly important for cognitive processes and emotional regulation, and would be of interest to investigate. Another advantage of MRI is that since it can record both functional and structural data, functional images can be superimposed onto the structural scan.

Rs-fMRI holds several advantages for studying psychosis in AD. One advantage is that it is

not subject to performance confounds introduced by tasks, which is particularly practical in cognitively impaired patient groups. Also, intrinsic connectivity networks (ICNs) identified at rest have been found to be active during tasks, suggesting that there is a correlation between resting-state and task-positive networks (Damoiseaux et al., 2006; Fox et al., 2006; Seeley et al., 2007; Toro et al., 2008).

Some limitations of MRI are the high cost; its susceptibility to motion artifacts; discomfort as individuals must lie on their backs in a tight enclosed space; loudness of the machine; and persons with certain metals in their bodies cannot undergo the scan. Moreover, individuals with significant agitation, claustrophobia and pain are precluded. Although MRI is susceptible to motion artifacts, there are robust preprocessing techniques available that can correct for motion and increase the signal-to-noise ratio. A limitation of rs-fMRI is that the unconstrained task (i.e. no external stimuli) may prompt over-interpretation of results that cannot be fully validated without cognitive or behavioural data.

1.4 Neuroimaging of delusions in AD

1.4.1. Structural Imaging of Delusions

Studies investigating the neuroanatomical changes associated with delusions in AD have shown variable results. Structural imaging studies using CT scans have generally found that delusions in AD are related to degeneration of the right frontal lobe (Burns et al., 1994; Forstl et al., 1991; Ismail et al., 2012). Forstl et al. found that AD patients with misidentification delusions (n=40) had significantly larger right anterior horn areas of the lateral ventricle and larger left anterior brain areas than patients without delusions (n=88) (Forstl et al., 1991). The authors concluded that atrophy in the right frontal lobe, with left sided preservation, is associated with misidentification delusions in AD. Burns et al. (1994) found that moderate-to-severe AD patients with misidentification delusions (n=15) had greater right frontal atrophy compared to non-delusional patients (n=41).

Geroldi et al. found that mild AD patients with paranoid delusions (n=19) had asymmetric volume loss of the right temporal and left frontal areas, in contrast to non-delusional patients (n=22) who showed symmetrical atrophy (Geroldi et al., 2002).

Data available from MRI studies, which have greater contrast, have localized frontal atrophy to more specific regions, but have also implicated multiple additional brain regions in association with delusions. Bruen et al. using VBM found that mild AD patients with misidentification delusions, delusional memories, or confabulations (n=5) had decreased grey matter density in the right IPL, bilateral inferior frontal gyrus, left medial frontal gyrus, and left claustrum compared to non-delusional patients (n=26)(Bruen et al., 2008). The study was well designed in controlling for age, years of education, and MMSE scores as covariates in the model. However whole brain volumes were not included, and including subjects with confabulations was a potential confounding factor. Serra et al., in a sample of amnesic MCI (aMCI) and mild-to-moderate AD patients, found that patients with misidentification delusions and content-based confabulations (n=5) showed decreased grey matter of the right hippocampus compared to patients without delusions (n=22) (Serra et al., 2010). Other areas that did not survive family-wise error (FEW) corrections include decreased grey matter of the right middle frontal gyrus, right parietal cortex, and the right precuneus. The authors included age, years of education, gender, and intra-cranial volumes as covariates in the VBM analysis, but the inclusion of patients with confabulations as well as patients with aMCI served as potential confounds. Whitehead et al. investigated regional cortical thickness and volume associated with paranoid delusions in mild-to-moderate AD (n=113, including 23 delusional and 90 non-delusional subjects) (Whitehead et al., 2012). They found that the female subjects with delusions (n=17) had reduced cortical thickness of the left medial orbitofrontal and left superior temporal compared to non-delusional female subjects (n=59), while there were no significant associations for male subjects, possibly due to the lower sample size. However, when the multivariate analysis accounted for global cognition as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), the difference associated with delusions

in females became non-significance. Ting et al. in a sample of MCI and AD subjects found that those with delusions (n=29) had reduced grey matter in 15 clusters, including the right precentral, right inferior frontal, right insula, and left middle occipital regions, compared to matched subjects without delusions (n=29) (Ting et al., 2015). Ting et al. included total intracranial volume as a covariate, but did not factor global cognition into the model. Makovac et al. correlated behavioural and psychological symptoms of dementia (BPSD) in AD with grey matter atrophy and found that the psychosis cluster (n=16) was correlated with grey matter atrophy in the orbitofrontal cortex, anterior cingulate cortex, and thalamus after covarying for age, years of education, gender, and MMSE scores (Makovac et al., 2016). However, the study did not separate delusions and hallucinations. Nakaaki et al. used VBM to compare the baseline brain differences between AD patients who did (n=18) and did not develop delusions (n=35) after correcting for total brain volume, age, gender, years of education, disease duration, and MMSE scores (Nakaaki et al., 2013b). Prior to the onset of delusions, the patients who developed delusions had smaller grey matter volumes in the bilateral parahippocampal gyrus (Brodmann 19, 30), the right orbitofrontal cortex (Brodmann 11), bilateral inferior frontal gyrus (Brodmann 44, 47), the right anterior cingulate (Brodmann 11), and the left insula (Brodmann 13). The delusional patients also had greater grey matter volumes in the right cerebellum, left lingual gyrus (Brodmann 18), left inferior temporal gyrus (Brodmann 20), and left occipital cortex (Brodmann 37). These brain differences however, were prior to the onset of delusions, and neither the post-delusional differences, nor the longitudinal brain changes, have been examined. In addition, the follow-up period was limited to 2 years, so it is possible that patients could develop delusions past the 2-year mark. Lastly, the sample was predominantly female (73.6%), which may have skewed the findings. Overall, the small sample sizes and variability in methodology in these MRI studies, such as differences in the covariates, could have contributed to the inconsistent findings across studies. The studies that identified brain regions that were more consistently found have accounted for total brain volume or cognition, and have comparatively larger sample sizes.

There have only been a handful of longitudinal studies looking at the changes over time (Fischer et al., 2016; Rafii et al., 2014). Rafii et al. correlated psychotic symptom severity with rates of neocortical atrophy in one year in 47 MCI and AD patients who were psychotic at baseline, and found that psychosis severity correlated with increased atrophy rates in the anterior cingulate, entorhinal, lateral frontal, medial orbitofrontal, and posterior cingulate gyri (Rafii et al., 2014). There were however some limitations, such as including a heterogeneous sample of MCI *and* AD patients, which could have confounded the results, as atrophy rates associated with delusions could be different in these patients populations. In addition, 7 *a priori* ROIs were used, which limited the investigation of structural changes to these areas rather than a more objective investigation of the entire cortex. The inclusion criteria for the psychotic group was also broad, consisting of any combination of delusion, hallucination, agitation, and wandering on the NPI, or any patients who used anti-psychotic medications. As different psychosis endophenotypes may have different neural mechanisms, the results may not be delusion-specific. Lastly, neuroanatomical changes were only measured in those who endorsed psychosis at baseline, which could have missed patients who later developed psychosis. In the only other longitudinal study, Fischer et al. compared pre- and post-delusional MRI scans of 24 patients with MCI at baseline and found decreased grey matter volume in the cerebellum and left posterior hemisphere following the onset of delusions (Fischer et al., 2016). However, as only 17 patients progressed to AD while 7 remained at the MCI stage at the post-delusional scan, the heterogeneous sample again may have confounded results. Moreover, it is possible that structural changes reflected Alzheimer disease progression rather than delusions, so it is important to compare the grey matter changes to a control group of non-psychotic subjects. Overall, the most consistent regions in association with delusions from MRI studies appear to be the frontal cortex (orbitofrontal, dorsolateral prefrontal cortex, inferior frontal cortex), parietal cortex, and anterior cingulate cortices without asymmetry.

In addition to grey matter structural differences, white matter differences have been observed on MRI. Lee et al. explored the relationship WMH and neuropsychiatric symptoms in 55 AD subjects, and found that psychotic symptoms were associated with white matter changes in the bilateral frontal, parieto-occipital, and the left basal ganglia regions (Lee et al., 2006). The effects were driven by patients with misidentification delusions, and were not associated with paranoid delusions or hallucinations. Ogawa et al. looked at the relationship between small blood vessel disease observed on MRI and BPSD in AD (Ogawa et al., 2013). They found that patients with small vessel disease (SVD) had significantly more delusions and depression than patients without SVD. Nakaaki et al. used DTI to investigate the relationship between white matter abnormalities and delusions in AD, and found that patients with delusions (n=10) displayed decreased fractional anisotropy (FA) in the left parieto-occipital and several connecting fibers, including the left inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the posterior corona radiata, and the forceps major of the corpus callosum (Nakaaki et al., 2013a). Makovac et al., also using DTI tractography, found white matter damage of the corpus callosum in psychotic AD subjects (Makovac et al., 2016). On the other hand, Howanitz and colleagues did not find any difference in WMH between delusional and non-delusional AD patients (Howanitz et al., 1995). The negative association between WMH and psychosis was also reported by Hirono et al. (Hirono et al., 2000). They found that WMH was related to some neuropsychiatric behaviours, although neither delusions nor hallucinations were significantly associated. Similarly, Berlow and colleagues investigated WMH and neuropsychiatric symptoms in 37 AD subjects, and found that WMH were related to anxiety, aberrant motor behaviour, and night-time behaviour, but not delusions or hallucinations (Berlow et al., 2010). Furthermore, Barber and colleagues found that an *absence* of WHM in the occipital lobe was related to delusions and hallucinations in Lewy body dementia (Barber et al., 1999). DeMichele-Sweet et al. examined the clinical and neuroimaging correlates of psychosis in AD, and did not find increased vascular risk factors or vascular lesions in psychotic patients (Demichele-Sweet et al., 2011).

1.4.2 Functional Imaging of Delusions

With regards to functional imaging investigations of delusions in AD, SPECT studies have found decreased metabolism primarily in the right frontal lobe (Lee et al., 2009; Matsuoka et al., 2010; Mega et al., 2000; Moran et al., 2008; Nakano et al., 2006; Nomura et al., 2012; Staff et al., 1999; Staff et al., 2000), left frontal lobe (Kotrla et al., 1995b; Mega et al., 2000), and right temporal lobe (Moran et al., 2008; Nakano et al., 2006; Nomura et al., 2012; Ponton et al., 1995; Starkstein et al., 1994), although the right parietal lobe has been implicated as well (Fukuhara et al., 2001; Kotrla et al., 1995b; Nakano et al., 2006). Some SPECT studies have also reported sex differences: Moran et al. (Moran et al., 2008) found that only male psychotic AD patients showed hypoperfusion in the right striatum while Matsuoka (Matsuoka et al., 2010) reported that only female psychotic AD patients showed hypoperfusion in the right insula. It should be noted that Mega and Matsuoka grouped delusions and hallucinations together as psychosis.

Studies using PET, which has greater contrast and spatial resolution than SPECT, have reported metabolic changes in multiple regions in association with delusions, including the frontal (Geroldi et al., 2002; Grady et al., 1990; Koppel et al., 2014c; Lopez et al., 2001; Mentis et al., 1995; Sultzer et al., 2003; Sultzer et al., 1995), parietal (Grady et al., 1990; Lopez et al., 2001; Mentis et al., 1995), medial occipital (Hirono et al., 1998a), medial temporal (Geroldi et al., 2002; Grady et al., 1990), and anterior cingulate regions (Ismail et al., 2012). Unlike SPECT studies, which predominantly showed right-sided hypometabolism, the laterality in PET studies remains mixed. Furthermore, some PET studies found *increased* metabolism in certain sensory association areas (Ismail et al., 2012).

1.4.3 Resting-state imaging of delusions in AD

With the emergence of rs-fMRI, researchers have begun to explore brain circuitry alterations in relation to neuropsychiatric disorders and symptoms. Connectivity within

the DMN has garnered particular interest because i) it is implicated in processing internal stimuli and representation of the self, ii) of its position as an information hub, and iii) this network is robustly detected across both healthy subjects and disease populations (Hu et al.).

Patients with AD have been found to show hypoconnectivity within the DMN (Agosta et al., 2012; Chhatwal et al., 2013; Greicius et al., 2004; Liu et al., 2014; Thomas et al., 2014; Zhang et al., 2010; Zhou et al., 2015a), and increased connectivity in the SN (Zhou et al., 2010). Greicius et al., using ICA to derive the DMN, found reduced resting-state connectivity of the posterior cingulate and hippocampus in a group of 13 mild AD subjects compared to 13 age-matched controls (Greicius et al., 2004). Zhang et al. investigated PCC resting-state functional connectivity changes in 46 AD patients, and similarly found reduced connectivity between the PCC and left hippocampus, and also decreased connectivity of the bilateral visual cortex, inferior temporal cortex, and right IPL with the right dorsolateral prefrontal cortex, ventral medial prefrontal cortex, and precuneus (Zhang et al., 2010). The changes were already evident in the mild AD group compared to controls, and the disconnectivity continued to intensify as AD progressed. Interestingly, Zhang et al. also found increased connectivity in the lateral frontoparietal regions. Agosta et al. (2012) explored connectivity patterns of the DMN, frontoparietal network, CEN, and SN in 13 AD patients, 12 amnesic MCI patients, and 13 controls, and found that AD was associated with decreased DMN and increased frontal network connectivity compared to controls, and reduced precuneus connectivity in aMCI compared to controls (Agosta et al., 2012). Liu et al. explored resting-state functional connectivity in AD (n=35) compared to healthy age-matched controls (n=21), and found reduced strength of the DMN in patients with AD, including of the medial PPC and dorsal medial prefrontal cortex (Liu et al., 2014). DMN nodes that are further apart were found to have more attenuated connectivity. Liu et al. also found that attenuation in DMN was correlated with dementia severity, with the greatest attenuation in severe AD patients (n=18), followed by mild AD (n=17), then amnesic MCI patients (n=18). Zhou et al. found that AD patients showed decreased functional connectivity between the thalamus and regions of the DMN and increased SN and thalamocortical connectivity (Zhou et al.,

2013). Zou et al. investigated whole-brain functional connectivity patterns in patients with AD and MCI and found decreased functional connectivity of the DMN and temporal lobe in the AD group (Zou et al., 2015). Koch et al. used a multivariate analysis approach combining ICA and 2 ROIs within the DMN to investigate the DMN connectivity in 15 AD subjects. They found that the DMN had a diagnostic power of 97% in predicting AD (Koch et al., 2012).

With regards to the relationship between network connectivity and clinical correlates, Thomas et al. (2014) found that clinical dementia rating (CDR) scores (higher scores indicates greater dementia severity) were negatively correlated with intra-network functional connectivity in the DMN, dorsal attention network, and CEN, and was not significantly related to SN or sensorimotor network connectivity (Thomas et al., 2014). Thomas et al. also found that CDR scores were anti-correlated with inter-network functional connectivity of the DMN with the dorsal attention network, and CEN with sensorimotor network. Different patterns of RSN connectivity may give rise to different cognitive deficits: executive control and episodic memory appear to be related to reduced functional connectivity of the frontal cortex while visuospatial impairments may be correlated with reduced functional connectivity of the IPL (Lehmann et al., 2015; Ranasinghe et al., 2014).

Evidently, there is a wide body of literature supporting that AD is associated with alternations in large-scale functional brain networks, particularly in the DMN but may extend to other networks. DMN, especially the PCC, may be especially susceptible to pathology due to their high glucose metabolism. Brain regions with higher metabolism have higher microglial activity, which releases proinflammatory properties that increases A β accumulation (Cagnin et al., 2001; Chen et al., 2006b; Richard et al., 2008; Tahara et al., 2006). Therefore, regions of high glucose metabolism, such as nodes of the DMN, may be more vulnerable to the pathological process of AD.

A growing number of studies are also beginning to connect the relationship between aberrant brain networks and neuropsychiatric symptoms within AD (Dichter et al., 2015;

Greicius 2008; Grupe & Nitschke 2013; Hamon & Blier 2013; Menon 2011; Price & Drevets 2010; Price & Drevets 2012; Seeley et al., 2007; Tromp et al., 2012; Uhlhaas 2013). However neuropsychiatric symptoms describe a range of heterogeneous symptoms and behaviour. There is only one study to date that investigated functional connectivity associated with neuropsychiatric symptoms in AD that included psychosis (Balthazar et al., 2014). Balthazar et al. correlated NPI scores with connectivity of the ventral and dorsal DMN and anterior and posterior SN in patients with AD, and only found a significant correlation with hyperactivity syndrome. However, their study combined patients with delusions (n=2), hallucinations (n=2), and night-time behaviours (n=6) into a single “psychosis cluster”. Given that most of the subjects in the psychosis group only had night-time behaviours and the sample size of subjects with delusions was extremely small, the findings are not specific enough for delusions.

1.4.4 Neuroimaging of delusion summary

Neuroimaging studies suggest that delusions in AD involve both structural and functional changes. Although the evidence is inconsistent, delusions appear to be associated with reduced grey matter volume, perfusion, or metabolism in the frontal cortex, anterior cingulate cortex (ACC), and insula (Brien et al., 2008; Koppel et al., 2014c; Matsuoka et al., 2010; Mega et al., 2000; Nakaaki et al., 2013b; Rafii et al., 2014; Sultzer et al., 2003; Whitehead et al., 2012). More specifically, frontal abnormalities may be localized to the orbitofrontal cortex (Koppel et al., 2014c; Makovac et al., 2016; Nakaaki et al., 2013b; Rafii et al., 2014; Whitehead et al., 2012), dorsolateral prefrontal cortex (Lopez et al., 2001; Mega et al., 2000; Sultzer et al., 2003), and inferior frontal cortex (Brien et al., 2008; Nakaaki et al., 2013b; Sultzer et al., 2003; Ting et al., 2015). Lateralization of the changes is unclear, with some reporting right-sided abnormalities (Nakaaki et al., 2013b; Sultzer et al., 2003) and others reporting left-sided abnormalities (Whitehead et al., 2012). Abnormalities in functional connectivity have not been explored in the context of delusions in AD, but its

investigation may lead to critical insights into the underlying neurobiology.

1.5 Knowledge Gaps

Understanding the neurobiological underpinnings of delusions is a critical issue for AD patients and their families. The lack of effective and safe treatments for this symptom is a major gap that can only be addressed through greater elucidation of the underlying mechanism. Neuropathology and neuroimaging are key components in achieving this. Research to date has yet to reach a conclusion regarding the neuropathological and neuroimaging correlates of delusions in AD. Converging evidence across different neuropsychiatric conditions suggests that frontal lobe deficits as well as RSN dysfunction are important neurobiological correlates of delusions. The inconsistencies in the literature regarding the neuropathological and neuroimaging correlates of delusions may be in part be due to assessing psychosis as a whole rather than separating psychosis into delusions and hallucinations. Increasing evidence suggests that the two endophenotypes have distinct mechanisms with separate clinical trajectories, and therefore research should investigate the neural correlates pertaining to each specific syndrome separately.

Chapter 2:

Specific Research Questions & Hypothesis

2.1 Summary and Rationale

Dementia is an extremely prevalent disorder, affecting nearly fifty million people worldwide, and the prevalence is expected to triple by the year 2050 (World Health Organization 2015). AD is the most common cause of dementia, accounting for 60-80% of all cases (Alzheimer's Association 2016). Psychotic symptoms frequently co-exist with cognitive deficits. It is estimated that a third of AD patients develop delusions and another sixth develop hallucinations throughout the course of the illness (Ropacki & Jeste 2005). Psychosis in AD is a marker of worse prognosis, including greater cognitive and functional deficits, hastened decline, greater caregiver stress and burden, higher hospitalization and institutionalization, and increased mortality (Fischer & Sweet 2016). There is increasing evidence from clinical and neuroimaging studies supporting that psychosis is heterogeneous, with delusions and hallucinations having distinct neurobiology. Delusion is the more common form of psychosis in AD, and its clinical significance renders it an important area of investigation in AD.

Despite its high prevalence and its link with adverse health outcomes, the pathophysiological and neuroanatomical correlates of delusions are not well understood in this patient population, hence limiting our ability to subsequently manage and treat these symptoms. The current antipsychotic medication being used was designed for schizophrenia patients, and has been repurposed for AD patients, which could explain the low efficacy and high adverse effects in this patient population (Schneider et al., 2005). The

lack of effective and safe treatments represents a major gap that needs to be tackled through better understanding of disease mechanisms and neural correlates of delusions.

While some clinical and cognitive correlates have been established, the neuropathologic and neuroimaging correlates of delusions are unclear. Several neuropathological studies have found that psychotic AD patients carry higher burden of AD disease pathology, including higher levels of senile plaque density and neurofibrillary tangles (Farber et al., 2000; Koppel et al., 2014a; Koppel et al., 2013; Murray et al., 2014a; Zubenko et al., 1991). These findings suggest that psychosis is a more severe form of AD. In contrast, other studies, including ones that accounted for co-morbid Lewy bodies, did not find an association between psychosis and increased AD pathology load (Skogseth et al., 2008; Sweet et al., 2000). Therefore, research to date has yet to reach a conclusion regarding the neuropathological correlates of psychosis in AD, although it is possible based on prior studies that Alzheimer pathology, cerebrovascular disease and Lewy bodies may all play a role. Limitations of previous studies include the fact that very few studies distinguished delusions from hallucinations; the sample sizes were small in many cases; most studies excluded analyses of vascular pathology; and correlations were made to clinical diagnosis without neuropathological confirmation. Post-mortem examinations of the brain is invaluable in elucidating the pathology of psychosis, but neuroimaging tools hold exceptional potential in revealing the brain architecture and function in living patients, which is crucial for the development of novel therapies.

Neuroimaging studies have begun to investigate the structural and functional changes associate with delusions, but with variable findings. CT and SPECT studies have implicated atrophy and hypoperfusion, respectively, in the right frontal and temporal lobes. However, studies using MRI and PET, which have greater contrast resolution, have implicated a variety of additional areas. Overall, delusions appear to be associated with reduced grey matter volume, perfusion, or metabolism in the frontal cortex, ACC, and insula (Brien et al., 2008; Koppel et al., 2014c; Matsuoka et al., 2010; Mega et al., 2000; Nakaaki et al., 2013b;

Rafii et al., 2014; Sultzer et al., 2003; Whitehead et al., 2012). With respect to lateralization, CT and SPECT studies found predominantly right-sided changes. However, studies utilizing MRI and PET did not find lateralization. One of the major factors contributing to the variability in the literature is that psychosis is often considered a single entity rather than a heterogeneous cluster of symptoms consisting of delusions and hallucinations. Moreover, there has only been one longitudinal study to date looking at grey matter changes pre- and post-delusions (Fischer et al., 2016). However, some limitations such as combining both AD and MCI patient cohorts and not having a control sample may have confounded the results. It is also possible that the structural changes may occur predating the clinical onset of delusions. Only one study has looked at the baseline pre-delusional brain changes, but did not follow the changes over time (Nakaaki et al., 2013b).

Moving beyond localized brain alterations, large-scale brain networks may hold the key in understanding higher order cognitive abilities and their breakdown. Converging evidence from other neuropsychiatric disorders with psychotic features have discovered disruptions in resting-state functional connectivity. These studies suggest that resting-state alterations may be a unifying explanation for psychosis. Abnormalities in resting-state functional connectivity have not been explored in the context of delusions within AD, and its investigation may lead to critical insights into the neurobiology underlying delusions.

This study aims to determine the neural correlates of delusions in AD, including greater understanding of neuropathological and neuroimaging changes. This is the first study to investigate the functional brain changes in AD patients with delusions using rs-fMRI.

2.2 Research Objectives and Hypotheses

The primary aims of this thesis are to determine the neuropathological correlates of psychosis and delusions in AD (2.2.1); the grey matter changes associated with delusions in AD, both cross-sectionally and longitudinally (2.2.2); and the functional resting-state connectivity changes associated with delusions in AD (2.2.3).

2.2.1 Investigate the neuropathological correlates of psychosis

Part one of the thesis is to investigate the neuropathological correlates of psychosis. The following objectives and hypotheses will be addressed in Chapter 3 of the current thesis.

The objectives are:

- 1) To determine if psychosis, stratified into delusions and hallucinations, is associated with increased markers of AD pathology (amyloid plaques and neurofibrillary tangles).
- 2) To compare the findings between clinically diagnosed AD and neuropathologically confirmed patients.
- 3) To investigate if Lewy body pathology and vascular pathology contribute to the genesis of psychosis.

The hypotheses associated with these objectives are:

- 1) Given that psychosis is associated with greater cognitive and functional impairments, we predict that patients with psychosis will have increased AD pathology burden (i.e. greater amyloid plaques and neurofibrillary tangles) compared to patients without any history of psychosis.
- 2) Given that up to 23% of AD patients do not have the corresponding neuropathology (Beach et al., 2012), we predict that patients with a clinical diagnosis AD will show different pathological correlates than patients with a neuropathological diagnosis of AD.
- 3) Given that Lewy body pathology is a characteristic feature of DLB as well PDD, two disorders where psychosis is particularly common, we hypothesize that Lewy bodies will be linked to psychosis in patients with AD. In addition, as white matter hyperintensities have been linked to psychotic symptoms (Lee et al., 2006), we hypothesize that there will be greater vascular pathology including greater lacunes, microinfarcts, arteriosclerosis, and arteriosclerotic leukoencephalopathy in patients with psychosis. By the same notion we hypothesize that there will be a more prevalent history of cardiovascular risk factors in patients with psychosis compared to patients without psychosis.

2.2.2 Investigating the structural changes associated with delusions in AD

Part two of the thesis is to investigate the structural brain differences associated with delusions in AD. The following objectives and hypotheses will be addressed in Chapter 4 of the current thesis.

The objectives are:

- 1) To identify the grey matter differences between delusional and non-delusional AD patients both before, as well as after, the clinical development of delusions.
- 2) To longitudinally assess the grey matter changes pre- and post- development of delusions, and to compare the changes to AD patients who do not develop delusions.

The hypotheses associated with these objectives are:

- 1) Given the association between delusions and frontal atrophy in the literature, we predict that patients with delusions will have reduced grey matter volume in frontal regions compared to patients without delusions. We hypothesize that these differences will already be present before the onset of delusions.
- 2) Given that patients with delusions show a more rapid cognitive decline (Ropacki & Jeste 2005), we predict that delusional patients will show more areas of atrophy, particularly in the inferior, orbitofrontal, and dorsolateral prefrontal cortex of the frontal lobe, compared to non-delusional patients over the course of follow-up.

2.2.3 Identify the resting-state functional connectivity changes associated with delusions in AD

Part three of the thesis is to explore the functional resting-state connectivity across large networks in AD patients with delusions. The following objective and hypothesis will be addressed in Chapter 5 of the current thesis.

The objective is:

To measure differences in spontaneous fluctuations in resting brain function in delusional relative to non-delusional AD patients.

The hypothesis associated with the objective is:

Given 1) that abnormal DMN have been previously reported in AD patients with neuropsychiatric symptoms as well as in other psychiatric populations, and 2) the results of Chapter 4 of the thesis, we predict that patients with delusions will have decreased functional connectivity between nodes of the DMN compared to patients without delusions.

Chapter 3:

Neuropathological correlates of psychosis

Chapter 3 of the current thesis has been peer-reviewed and published:

Fischer CE, **Qian W**, Schweizer TA, Millikin CP, Ismail Z, Smith EE, Lix LM, Shelton P, Munoz DG. (2016). Lewy bodies, vascular risk factors and Subcortical Arteriosclerotic Leukoencephalopathy, but not Alzheimer lesion load, are associated with the development of psychosis in Alzheimer's disease. *Journal of Alzheimer's Disease*, 50(1):283-95. PMID: 26682680

Several studies have investigated the pathological association of psychosis with markers of AD pathology, including amyloid-beta and tau pathology, as well as with Lewy bodies and vascular lesions. However, the evidence remains mixed. Earlier studies have found that severe amyloid-beta pathology, in the form of neuritic plaques, contribute to psychosis in AD (Forstl et al., 1993b; Zubenko et al., 1991), but more recent studies that accounted for Lewy bodies did not find an association (Sweet et al., 2000). There have been slightly more consistency implicating protein tau pathology in psychosis, with most studies finding an association (Forstl et al., 1993b; Koppel et al., 2014a; Koppel et al., 2013; Murray et al., 2014a; Zubenko et al., 1991), even after accounting for comorbid Lewy body pathology (Farber et al., 2000). However, some studies did not find such an association between tau and psychosis (Jacobson et al., 2014; Skogseth et al., 2008; Sweet et al., 2000). Many of these past studies have been limited in sample size and used a clinical diagnosis of AD rather than a pathological diagnosis. Given that psychosis, specifically hallucinations, is one of the criteria for the clinical diagnosis of DLB, and that Lewy bodies may occur in half of all neuropathologically confirmed AD patients (Hamilton 2000), it is highly possible that Lewy bodies may contribute to psychosis in AD. Vascular lesions on MRI have also been implicated in the development of late-onset psychosis (Breitner et al., 1990), but more recent studies did not find an association with vascular lesions or risk factors in association

with psychosis (Demichele-Sweet et al., 2011). However vascular entities on pathology have not been investigated.

Chapter 3 of the current thesis aimed to identify the neuropathological correlates of psychosis, subdivided into delusions and hallucinations. The association between AD pathology, Lewy body pathology, and vascular pathology will be investigated.

3.1 Experimental Materials and Methods

3.1.1 Statement of Ethical Approval

Ethical approval for the current study was obtained from the Research Ethics Board (REB) at St. Michael's Hospital, Toronto Canada under REB 13-131 entitled, "Neuroimaging Profiles of Neuropsychiatric Subgroups in Mild Cognitive Impairment and Dementia".

3.1.2 Data source

Data for the neuropathology analysis were obtained from the National Alzheimer's Coordinating Center (NACC) (Beekly et al., 2007), so we were limited to the scales that were already collected. The NACC database is a secondary database that combines data from past and present Alzheimer's Disease Centers (ADCs). Established in 1999, the NACC database has since become one of the largest and most comprehensive databases in the world. NACC has an established, standardized protocol for data-collection for all the ADCs. The data collected is reliable and provides a comprehensive way to support collaborative research in neurodegenerative disease. Furthermore, NACC has quality assurance and quality control measures in place at each step of the data collection process, including

frequent review of the data to detect any inconsistent entries. The Uniform Data Set (UDS) collects prospective and longitudinal data since September 2005, and has gathered data on over 35,000 subjects as of June 2017. The Neuropathology Data (NP) dataset includes neuropathology data on over 15,000 subjects.

The current data were collected from 29 ADCs from September 2005 to May 2012. All participants in the database had standardized clinical evaluations and received follow-ups approximately annually for as long as the subject was able and willing to participate.

The following data from the UDS and NP data sets were analyzed from the UDS:

Demographic information including sex, years of education, and disease duration calculated from the age of cognitive decline (not age of dementia diagnosis) to age of death, based on a clinician's assessment.

Vascular risk factors including a history of hypertension, diabetes, hypercholesterolemia, and smoking. Vascular risk factors were classified as "absent/remote" or "recent/active".

Functional Activity Questionnaire (FAQ) (Pfeffer et al., 1982) is a brief questionnaire completed by a caregiver/family member, and inquires about activities of daily living (ADL). A higher score on the FAQ indicates greater functional impairment. The FAQ has fairly high correlation (0.72) with other functioning instruments (i.e. Lawton and Brody's Instrumental Activities of Daily Living). FAQ has excellent inter-rater reliability (0.97) (Pfeffer et al., 1982).

Mini-Mental State Examination (MMSE) (Folstein et al., 1975) is the most widely used screening assessment for cognitive impairment. The MMSE is out of 30, with a cut-off score of 23 or below indicating dementia. However the MMSE has been criticized for low sensitivity. A review of 4,248 individuals indicated that a cut-off of 27 would be more accurate, especially in highly educated individuals, in identifying those with dementia (O'Bryant et al., 2008). Nonetheless the MMSE has demonstrated high reliability and sensitivity in detecting moderate to severe AD (Tombaugh & McIntyre 1992). The MMSE is also a test recommended by the NINCDS-ADRDA in the diagnosis of probable AD (McKhann et al., 1984).

Clinical Dementia Rating (CDR)(Hughes et al., 1982) is a 5-point scale used to characterize the severity of AD. The 6 domains being examined are memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Information from these domains is obtained from an informant or collateral source. For each domain, a score of 0 indicates normal; 0.5 indicates very mild dementia, 1 indicates mild dementia; 2 indicates moderate dementia; and 3 indicates severe dementia.

Neuropsychiatric Inventory Questionnaire (NPI-Q) (Cummings et al., 1994) measures 12 categories of behavioural disturbances, and is completed by a caregiver. The presence of delusions and/or hallucinations was identified by the delusional and hallucination items from the questionnaire. The delusional item asks "Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?", while the hallucination item asks "Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?"

The following data were analyzed from the NP data set:

Braak & Braak stage is a criteria for classifying neurofibrillary tangles (NFTs) into 6 stages based on density and distribution (Braak & Braak 1991): stages I/II corresponds to NFTs predominantly in the entorhinal/transentorhinal cortex; stages III/IV corresponds to NFTs progressing to the limbic structures (hippocampus and amygdala), inferior structures of the temporal lobe, and nucleus basalis; and stages V/VI corresponds to NFTs distributed to the association neocortex, sparing motor and sensory cortices. In stages I/II, the individual is asymptomatic and does not have cognitive impairment; in stages III/IV, the individual has incipient AD with mild cognitive impairment; and in stages V/VI, the individual has dementia with more severe cognitive impairment. The Braak and Braak rating is based only on neuropathological changes without clinical correlates, and as such is usually adopted for research purposes. The Braak & Braak stage has good inter- and intra-rater reliability of 0.6-0.8 (Nagy et al., 1998). It has high specificity of 99.8% but low sensitivity of 69.7% (Murayama & Saito 2004).

Consortium to Establish a Registry of Alzheimer's Disease (CERAD) (Mirra et al., 1991) is a semiquantitative method for evaluating the extent of amyloid plaques in the brain. The CERAD considers the amyloid plaque density in the middle frontal, superior-middle temporal, and inferior parietal regions of the brain, and the cortical region that is most severely affected is used. CERAD classifies the density as none, sparse, moderate, or frequent. Neuritic plaques are considered plaques with argyrophilic, thioflavin-S-positive or tau-positive dystrophic neuritis with or without dense amyloid cores. The CERAD does not consider diffuse plaques or the age of individual, unlike in the original CERAD criteria.

NIA-Reagan Institute neuropathological criteria (Hyman & Trojanowski 1997) combine the CERAD and Braak stage in determining the probability of dementia being due to AD as either "not AD", "low", "intermediate", or "high" (Table 3.1). The criteria have been found to have high specificity but low sensitivity.

Table 3.1. NIA-Reagan institute neuropathological criteria for the likelihood of dementia due to AD, which combines CERAD scores with Braak neurofibrillary tangle stages.

		Braak Stages (Neurofibrillary tangles)						
		0	I	II	III	IV	V	VI
CERAD Score (Neuritic plaques)	Negative	Not AD						
	Infrequent		Low					
	Moderate				Intermediate			
	Frequent						High	

Criteria for Dementia with Lewy bodies (McKeith et al., 2005) is based on guidelines by McKeith et al. Immunohistochemistry assessment for synucleins is used as it is more specific than ubiquitin. Lewy body is assessed independently of AD pathology. The criteria consider a region to be Lewy body positive if there are more than 5 Lewy bodies per region. Lewy body follows a similar pattern of progression as NFTs outlined by Braak, typically starting in the brainstem (brainstem predominant type), spreading to the limbic structures (limbic type), and finally diffusely to the neocortex (neocortical type).

Vascular pathology evaluation included the presence or absence of any gross or microscopic vascular pathology, including lacunes (cystic/old infarcts or hemorrhages $\leq 1\text{cm}$ in diameter), cortical microinfarcts, hemorrhages, hippocampal sclerosis, and subcortical arteriosclerotic leukoencephalopathy (SAL—multifocal or diffuse white matter pathology attributable to arteriosclerotic small vessel disease (Caplan 1995; Roman 1987)).

3.1.3 Participants

Patients with a primary clinical diagnosis of probable AD (cAD) based on the NINCDS-ADRDA criteria (McKhann et al., 2011) with available pathologic data, and patients with a neuropathological diagnosis of AD (npAD) as defined by “Definite AD” on the CERAD criteria were included in the analysis. Brain injury, central nervous system (CNS) neoplasm, Down syndrome, Huntington’s disease and Prion disease were exclusion factors.

The presence of delusions or hallucinations was identified by a positive score on the NPI-Q) (Kaufer et al., 2000) delusional and hallucinatory items, respectively, at any of the visits. As the persistence of psychosis in AD is low and rarely persists after a few months (Ropacki & Jeste 2005), patients with psychotic symptoms at any visit were included in the psychotic group. Clinically diagnosed AD subjects with neither psychotic item endorsed at any visit were considered never psychotic (cAD-P) while subjects who had psychosis at any visit were considered psychotic (cAD+P). The cAD+P group was further classified into i) delusional (only the presence of delusions at any visit; cAD+D), ii) hallucinatory (only the presence of hallucinations; cAD+H), or iii) both delusions and hallucinations at any visit (cAD+DH). Neuropathologically confirmed AD subjects without any psychosis were designated as npAD-P while those with any history of psychosis were designated as npAD+P. Similarly, npAD+P patients were further classified into npAD+D for delusions, npAD+H for hallucinations, or npAD+DH for delusions *and* hallucinations (Figure 3.1).

3.1.4 Statistical Analysis

Objective 1

To determine if psychosis were associated with increased markers of AD pathology (objective 1), we statistically compared AD pathology load between non-psychotic (AD-P)

and psychotic subjects (AD+P). Psychotic subgroups (cAD+D, cAD+H, and cAD+DH) were individually compared to cAD-P using univariate tests. Ordinal logistic regression was used to test differences in Braak staging, CERAD, NIA-Reagan, and neuritic plaque density. As each psychotic subgroup was compared to the control group, multiple comparisons were corrected using Bonferroni corrections.

Objective 2

To compare if the findings in the clinical cohort were consistent in subjects with a neuropathologically confirmed AD (objective 2), npAD+D, npAD+H, and npAD+DH groups were individually compared to npAD-P subjects. As each psychotic subgroup was compared to the control group, multiple comparisons were corrected using Bonferroni corrections.

Objective 3

To investigate if other pathologies were related to psychosis, we statistically compared any difference in LB and vascular pathology between psychotic groups in the neuropathologically confirmed AD cohort. The χ^2 test of independence was used for categorical data and ordinal logistic regression was used for ordinal data. The categorical variables investigated include: gross/microscopic vascular pathology (yes/no), presence of microinfarcts (yes/no), lacunes (yes/no), hippocampal sclerosis (yes/no), hemorrhages (yes/no), subcortical arteriosclerotic leukoencephalopathy (yes/no), smoker (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), or diabetes (yes/no). Ordinal regression was used for Lewy bodies. Statistical significance was assessed using $\alpha=0.05$; multiple comparisons were not corrected, as the associations in objective 3 were exploratory.

Demographic data were compared using χ^2 test or the Mann-Whitney test for continuous data. With respect to the latter, a non-parametric test was adopted instead of the parametric t-test because Kolmogorov-Smirnov test of normality was statistically significant. Demographic data were not corrected for multiple comparisons because they were not part of the main objectives.

All statistical analysis was performed using SPSS version 21.

3.2 Results

3.2.1 Demographic and clinical variables

We identified 1073 subjects in the NACC database who fulfilled the criteria for analysis with available neuropathology data, including 890 cAD and 728 npAD subjects (Figure 3.1). The cAD and npAD groups overlapped, as not all the cAD subjects had a neuropathological diagnosis of AD. Of the npAD patients who were not clinically diagnosed with AD (false negatives, n=116), 42 (36.2%) were diagnosed with DLB, 11 (9.5%) were diagnosed with Parkinson's disease dementia, 12 (10.3%) were diagnosed with vascular dementia, and 51 (44.0%) were diagnosed with possible AD. The average MMSE score of the npAD group was 13.6 ± 8.0 , so the group appeared to meet the threshold for dementia.

In the npAD+D group, 121/140 (86.4%) patients exhibited active delusions at the last visit prior to death; in the npAD+H group, all 52 patients exhibited active hallucinations at the last visit prior to death; and in the npAD+DH group, 69/79 (87.3%) patients exhibited active delusions while all 79 patients exhibited active hallucinations at the last visit prior to death.

There were no statistically significant differences between cAD-P (Tables 3.2 and 3.4) and the cAD psychotic groups as well as between npAD-P (Tables 3.3 and 3.5) and the npAD psychosis groups with respect to age of death, years of education, ethnicity and sex. We looked at the relationship between psychotic symptoms and FAQ, MMSE and CDR on the last visit prior to death. AD+P groups did not differ from AD-P in both cAD and npAD cohorts on the MMSE, CDR, or FAQ but further breakdown of the psychotic groups showed that AD+H and AD+DH were associated with more cognitive impairments on the MMSE and CDR, as well as greater functional impairment on the FAQ compared to AD-P, although the npAD+DH group did not reach significance on the MMSE. On the contrary, AD+D cohorts were associated with less impairment than AD-P on global CDR. However, cAD+P, cAD+D, cAD+DH, and npAD+D patients had a significantly longer duration from last clinical visit to death than their respective non-psychotic control groups. In addition, cAD+P, cAD+D, and cAD+DH groups had longer disease durations compared to cAD-P.

3.2.2 Psychosis and AD load in clinically-diagnosed AD

Autopsy findings revealed that, compared to cAD-P, there was significantly higher Braak staging in cAD+P, cAD+D, and cAD+DH (Figure 3.2), more frequent neuritic plaques in cAD+P and cAD+D (Figure 3.3), as well as greater AD burden on the NIA-Reagan in all psychotic cAD groups (Figure 3.4; Table 3.4).

3.2.3 Psychosis and AD load in neuropathologically-diagnosed AD

In contrast, in the neuropathologically confirmed AD group, there were no significant differences in Braak stage, plaque count, or NIA-Reagan between npAD-P and any of the psychotic subgroups (Table 3.5).

3.2.4 Other pathologies associated with psychosis

We found significantly more extensive Lewy body pathology in npAD+P, npAD+H, and npAD+DH groups compared to npAD-P (Figure 3.5). There was a greater proportion of patients who had SAL in npAD+P and npAD+DH groups compared to the npAD-P group (Figure 3.6). There was no statistically significant association between psychosis and gross or microscopic vascular pathology, presence of microinfarcts, lacunes, hippocampal sclerosis, or hemorrhages.

Given the positive association between vascular pathology and psychosis, we also investigated the relation between vascular risk factors and psychosis. A history of hypertension was associated with npAD+P; and a history of diabetes was associated with npAD+DH (Figure 3.7).

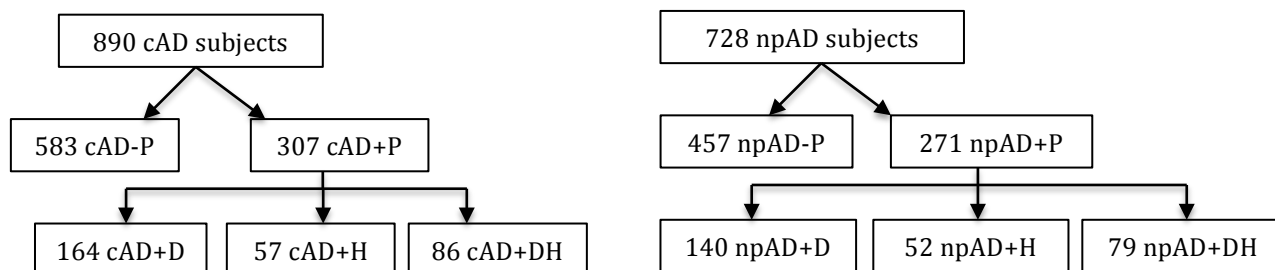


Figure 3.1. Distribution of clinically diagnosed (cAD) and neuropathologically confirmed (npAD) Alzheimer's disease subjects with neuropathological data into psychotic groups.

Table 3.2. Demographics, clinical, and pathological correlates of clinically diagnosed AD patients with and without psychosis

Variable	Psychosis status									
	cAD-P		cAD+P							
	<i>n</i> = 583 (66%)		<i>n</i> = 307 (34%)		cAD+D		cAD+H		cAD+DH	
	<i>N</i> / mean	% / SD	<i>N</i> / mean	% / SD	<i>n</i> = 164 (53%)		<i>n</i> = 58 (19%)		<i>n</i> = 86 (28%)	
					<i>N</i> / mean	% / SD	<i>N</i> / mean	% / SD	<i>N</i> / mean	% / SD
Age of death	81.3	10.0	80.1	10.5	80.7	10.9	79.8	9.6	79.4	10.2
Male	336	57.5%	158	51.5%	83	50.6%	30	51.7%	46	51.7%
Education (years)	15.0	3.3	14.9	3.2	15.1	3.1	15.1	2.5	14.3	3.8
Disease duration (years)	9.6	4.3	10.3*	4.3	10.3*	4.2	9.79	4.5	10.6*	4.4
Years between last clinical visit and death	1.45	1.51	1.78*	1.50	2.05*	1.55	1.28	1.15	1.63	1.50
CDR					*		*		*	
Severe impairment	230	39.4%	125	40.7%	46	28.0%	33	56.9%	46	53.5%
Moderate impairment	186	31.8%	112	36.5%	60	36.6%	19	32.8%	34	39.5%
Mild impairment	135	23.1%	61	19.9%	50	30.5%	5	8.6%	6	7.0%
Questionable impairment	33	5.7%	9	2.9%	8	4.9%	1	1.7%	0	0.0%
No impairment	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
MMSE	14.3	8.1	13.5	7.6	15.8	7.3	10.5*	8.1	10.2*	6.0
FAQ	26.8	5.3	27.7	4.0	26.4	4.9	29.0*	2.7	28.8*	2.4
Braak Stage			*		*				*	
6	265	45.6%	164	53.6%	90	54.9%	27	47.4%	48	55.8%

5	137	23.6%	89	29.1%	41	25.0%	22	38.6%	26	30.2%
4	78	13.4%	32	10.5%	20	12.2%	4	7.0%	8	9.3%
3	36	6.2%	7	2.3%	4	2.4%	3	5.3%	0	0%
2	27	4.6%	8	2.6%	5	3.0%	0	0%	3	3.5%
1	26	4.5%	2	.7%	2	1.2%	0	0%	0	0%
Criteria not met	12	2.1%	4	1.3%	2	1.2%	1	1.8%	1	1.2%
NIA-Reagan			*		*		*		*	
High	396	68.2%	244	79.7%	129	78.7%	47	82.5%	69	80.2%
Intermediate	92	15.8%	39	12.7%	23	14.0%	6	10.5%	10	11.6%
Low	33	5.7%	9	2.9%	4	2.4%	1	1.8%	4	4.7%
Not met	60	10.3%	14	4.6%	8	4.9%	3	5.3%	3	3.5%
CERAD			*		*		*		*	
Definite AD	389	70.3%	221	82.8%	122	84.7%	42	82.4%	58	79.5%
Probable AD	73	13.2%	26	9.7%	10	6.9%	7	13.7%	9	12.3%
Possible AD	28	5.1%	9	3.4%	5	3.5%	0	0%	4	5.5%
Criteria not met	63	11.4%	11	4.1%	7	4.9%	2	3.9%	2	2.7%
Neuritic Plaques			*		*					
Frequent	393	67.3%	228	74.3%	121	73.8%	44	75.9%	64	74.4%
Moderate	104	17.8%	61	19.9%	32	19.5%	11	19.0%	18	20.9%
Sparse	29	5.0%	9	2.9%	5	3.0%	1	1.7%	3	3.5%
None	58	9.9%	9	2.9%	6	3.7%	2	3.4%	1	1.2%

cAD-P Never psychotic; cAD+P psychosis; cAD+D delusional psychosis; cAD+H hallucinatory psychosis; cAD+DH delusional and hallucinatory psychosis

* Indicates significant difference compared to cAD-P, two-tailed, $p < 0.05$

Table 3.3. Demographics, clinical, pathological correlates, and vascular risk factors of neuropathologically definite AD patients with and without psychosis

Variable	Psychosis status									
	npAD-P		npAD+P							
	<i>n</i> = 457 (63%)		<i>n</i> = 271 (37%)		npAD+D		npAD+H		npAD+DH	
	<i>N</i> / mean	% / SD	<i>N</i> / mean	% / SD	<i>n</i> = 140 (52%)		<i>n</i> = 52 (19%)		<i>n</i> = 79 (29%)	
					<i>N</i> / mean	% / SD	<i>N</i> / mean	% / SD	<i>N</i> / mean	% / SD
Age of death	80.0	10.3	78.9	10.4	79.6	10.7	78.0	10.3	78.5	10.0
Male	260	56.9%	154	57%	76	54.3%	29	55.8%	50	63.3%
Education (years)	15.3	3.2	15.0	3.2	15.3	3.0	15.0	2.8	14.7	3.6
Disease duration (years)	9.8	3.9	9.9	3.9	10.1	4.0	9.6	4.3	9.7	3.7
Years between last clinical visit and death	1.54	1.58	1.81*	1.50	2.04*	1.55	1.29	1.14	1.75	1.52
CDR					*		*		*	
Severe impairment	196	42.9%	113	41.9%	40	28.6%	32	61.5%	41	51.9%
Moderate impairment	148	32.4%	103	38.1%	61	43.6%	15	28.8%	28	35.4%
Mild impairment	91	19.9%	46	17.0%	34	24.3%	2	3.8%	10	12.7%
Questionable impairment	22	4.8%	8	3.0%	5	3.6%	3	5.8%	0	0.0%
No impairment	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
MMSE	13.0	8.2	13.0	7.2	14.8	6.9	9.9*	8.1	11.0*	6.2
FAQ	27.1	5.2	27.8	4.0	26.8	4.6	28.4*	4.1	28.9*	2.3
Braak Stage										
6	271	59.3%	160	59.3%	87	62.1%	31	59.6%	43 %	54.4%

5	130	28.4%	90	33.3%	42	30.0%	18	34.6%	30 %	38.0%
4	43	9.4%	13	4.8%	6	4.3%	1	1.9%	6 %	7.6%
3	10	2.2%	2	.7%	1	.8%	1	1.9%	0 %	0%
2	2	0.4%	3	1.1%	2	1.4%	1	1.9%	0 %	0%
1	0	0%	1	.4%	1	.7%	0	0%	0 %	0%
Criteria not met	1	0.2%	1	.4%	1	.7%	0	0%	0 %	0%
NIA-Reagan										
High	412	90.2%	252	93.3%	131	93.6%	49	94.2%	73	92.4%
Intermediate	42	9.2%	12	4.4%	7	5.0%	1	1.9%	4	5.1%
Low	1	.2%	2	.7%	1	.7%	1	1.9%	0	0.0%
Not met	2	.4%	4	1.5%	1	.7%	1	1.9%	2	2.5%
Neuritic Plaques										
Frequent	425	93.0%	251	93.0%	131	93.6%	48	92.3%	73	92.4%
Moderate	31	6.8%	19	7.0%	9	6.4%	4	7.7%	6	7.6%
Sparse	1	.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
None	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Lewy Bodies			*				*		*	
Diffuse neocortical	62	15.2%	61	25.8%	24	18.8%	16	34.8%	21	33.3%
Limbic transitional	46	11.3%	30	12.7%	19	14.8%	3	6.5%	8	12.7%
Brainstem type	13	3.2%	11	4.7%	7	5.5%	2	4.3%	2	3.2%
No Lewy bodies	287	70.3%	134	56.8%	78	60.9%	25	54.3%	32	50.8%
SAL			*						*	
Yes	67	14.7%	64	23.8%	29	20.9%	12	23.1%	23	29.1%
No	388	85.3%	205	76.2%	110	79.1%	40	76.9%	56	70.9%
Smoker										
No	258	59.0%	140	52.4%	75	54.0%	29	56.9%	37	47.4%
Yes	179	41.0%	127	47.6%	64	46.0%	22	43.1%	41	52.6%
Hypertension			*							

Absent	246	56.6%	124	47.7%	64	47.1%	24	49.0%	37	48.7%
Active	189	43.4%	136	52.3%	72	52.9%	25	51.0%	39	51.3%
Hypercholesterolemia										
Absent	254	58.4%	135	52.7%	72	53.3%	25	54.3%	39	51.3%
Active	181	41.6%	121	47.3%	63	46.7%	21	45.7%	37	48.7%
Diabetes									*	
Absent	416	91.4%	233	87.3%	120	87.6%	48	92.3%	66	83.5%
Active	39	8.6%	34	12.7%	17	12.4%	4	7.7%	13	16.5%

npAD-P Never psychotic; npAD+P psychosis; npAD+D delusional psychosis; npAD+H hallucinatory psychosis; npAD+DH delusional and hallucinatory psychosis

* Indicates significant difference compared to npAD-P, two-tailed, $p < 0.05$

Table 3.4. Test statistics for significant variables comparing clinically diagnosed AD patients (cAD) with and without psychosis. The gray cells represent non-significant associations.

Variable	Psychosis status			
	cAD+P			
		cAD+D	cAD+H	cAD+DH
Disease duration (years)	U= 80640.0, p=0.034	U=42213.0, p=0.049		U=21532, p=0.05
Global CDR		OR of 1.451 (95% CI, -0.688 to -0.056, Wald χ^2 (1)=5.331, p=0.019	OR=0.444, 95% CI, 0.282 to 1.341, Wald χ^2 (1)=9.034, p=0.002	OR=0.459, 95% CI, 0.337 to 1.218, Wald χ^2 (1)=11.966, p<0.001
MMSE			U=5339.5, p=0.01	U=8188.5, p<0.001
FAQ	P=0.06		U=8092.0, p<0.001	U=14347, p=0.002
Braak Stage	OR=1.606, 95% CI, -	OR=0.631, 95% CI,		OR=0.562, 95% CI,

	0.737 to -0.211, Wald $\chi^2(1)=12.49$, $p<0.001$	0.128 to 0.791, Wald $\chi^2(1)=7.402$, $p=0.005$		0.136 to 1.017, Wald $\chi^2(1)$, $p=0.007$
NIA-Reagan	OR=0.5283, 95% CI, 0.311 to 0.965, Wald $\chi^2(1)=14.631$, $p<0.001$	OR= 1.788, 95% CI, -0.992 to -0.17, Wald $\chi^2(1)=7.666$, $p=0.004$	OR= 2.217, 95% CI, -1.498 to -0.094, Wald $\chi^2(1)=4.941$, $p=0.017$	OR= 1.925, 95% CI, -1.223 to -0.108, Wald $\chi^2(1)=5.468$, $p=0.013$
CERAD	OR=0.480, 95% CI, 0.368 to 1.098, Wald $\chi^2(1)=15.474$, $p<0.001$	OR= 2.337, 95% CI, -1.336 to - 0.363, Wald $\chi^2(1)=11.703$, $p<0.001$	OR= 2.086, 95% CI, -1.485 to 0.015, Wald $\chi^2(1)=3.687$, $p=0.036$	P=0.059
Neuritic Plaques	OR=0.656, 95% CI, 0.113 to 0.728, Wald $\chi^2(1)=7.205$, $p=0.006$	OR= 1.470, 95% CI, -0.772 to 0.003, Wald $\chi^2(1)=3.783$, $p=0.044$		

Table 3.5. Results of statistical analysis comparing neuropathologically diagnosed AD patients (npAD) with and without psychosis. The gray cells represent non-significant associations.

Variable	Psychosis status			
	npAD+P			
		npAD+D	npAD+H	npAD+DH
Global CDR		OR= 1.480, 95% CI, -0.74 to -0.045, Wald χ^2 (1)=4.903,p=0.024	OR=0.453, 95% CI, 0.218 to 1.365, Wald χ^2 (1)=7.307, p=0.005	OR=0.618, 95% CI, 0.024 to 0.939, Wald χ^2 (1)=4.258, p=0.033
MMSE			U=3860.5, p=0.035	U=7287, p=0.053
FAQ			U=6650.0, p=0.023	U=11632.0, p=0.02
Lewy Bodies	OR=1.825, 95% CI, -.927 to .278, Wald χ^2 (1)=13.255, p<0.001	OR=0.690, 95% CI, -0.33 to .775, Wald χ^2 (1)=3.235, p=0.073	OR=0.444, 95% CI, .223 to 1.399, Wald χ^2 (1)=7.309, p=0.01	OR=0.408, 95% CI, .385 to 1.408, Wald χ^2 (1)=11.808, p=0.001
Subcortical Arteriosclerotic Leukoencephalopathy	χ^2 (1, N=724)=9.377, p=0.002			χ^2 (1, N=533)=9.882, p=0.002
Hypertension	χ^2 (1, N=695)=5.131, p=0.024			χ^2 (1, N=570)=3.680, p=0.055
Hypercholesterolemia				
Diabetes				χ^2 (1, N=533)=4.728, p=0.03

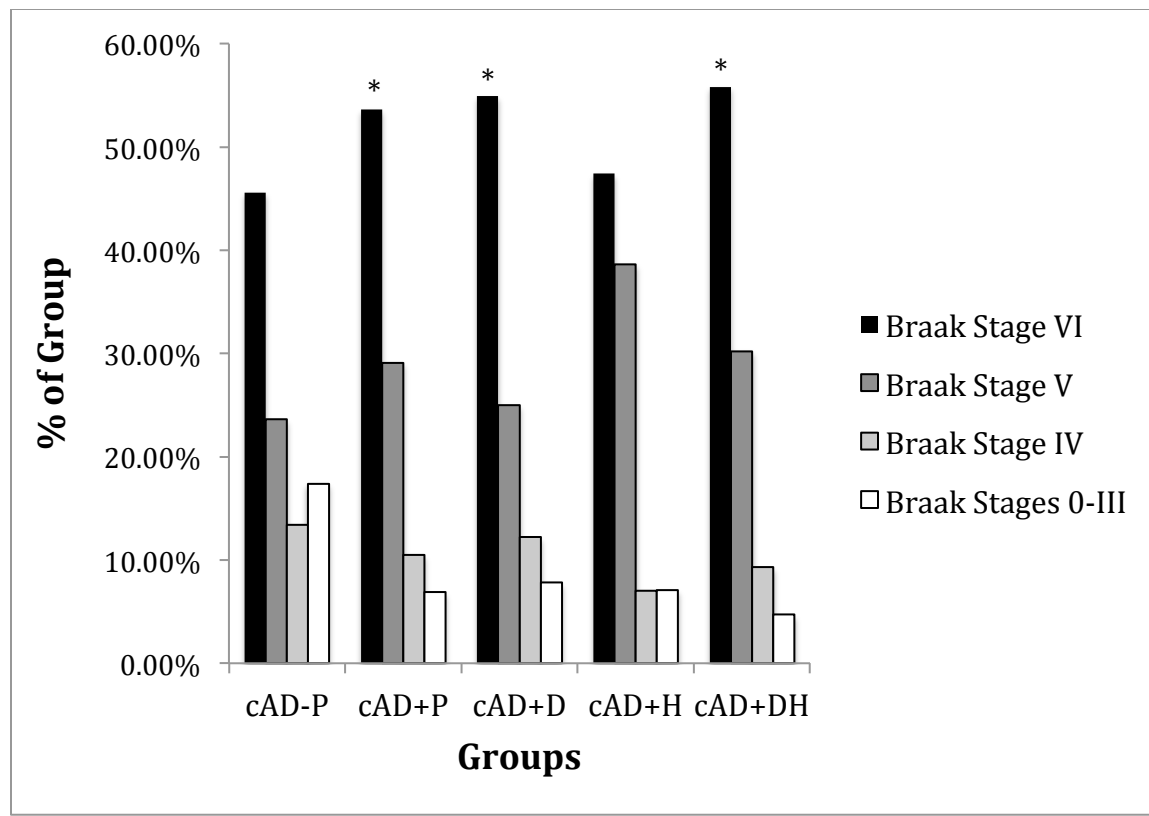


Figure 3.2. Braak staging between clinically diagnosed AD patients (cAD), subdivided into those without psychosis (cAD-P) and those with psychosis (cAD+P). The psychotic group was further divided into those with delusions (cAD+D), hallucinations (cAD+H), or both forms of psychosis (cAD+DH). Stages 0-III are combined to show the proportion of subjects with a clinical diagnosis of AD but who do not have neuropathological evidence of AD. * indicates statistical difference compared to the cAD-P group.

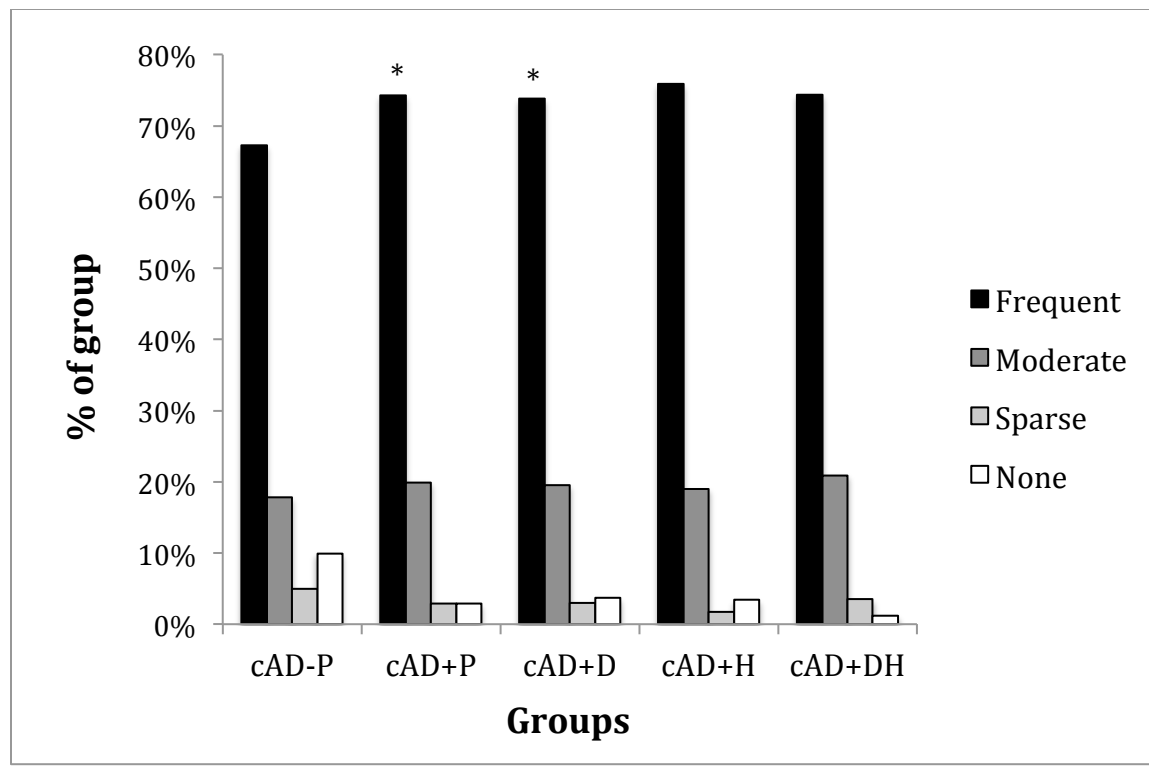


Figure 3.3. Neuritic plaque density between clinically diagnosed AD patients (cAD), subdivided into those without psychosis (cAD-P) and those with psychosis (cAD+P). The psychotic group was further divided into those with delusions (cAD+D), hallucinations (cAD+H), or both forms of psychosis (cAD+DH). * indicates statistical difference compared to the cAD-P group.

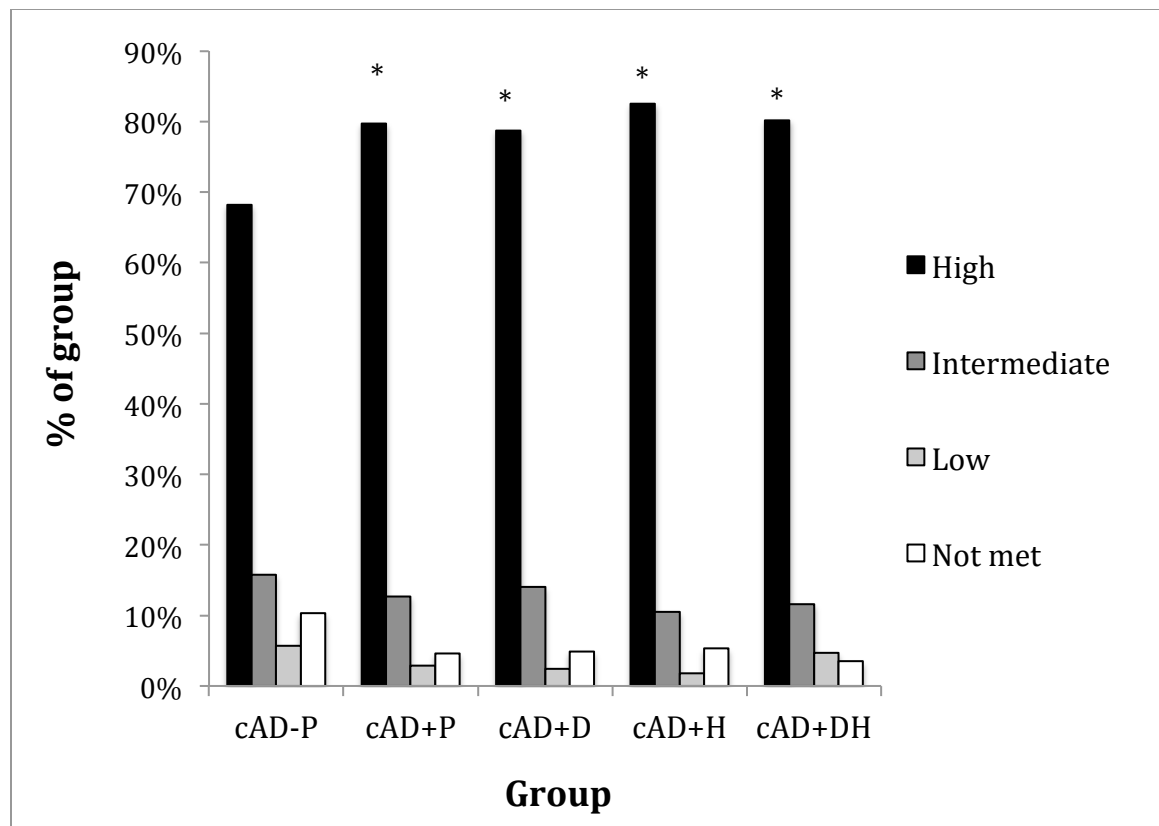


Figure 3.4. NIA-Reagan categorizations between clinically diagnosed AD patients (cAD), subdivided into those without psychosis (cAD-P) and those with psychosis (cAD+P). The psychotic group was further divided into those with delusions (cAD+D), hallucinations (cAD+H), or both forms of psychosis (cAD+DH). * indicates statistical difference compared to the cAD-P group.

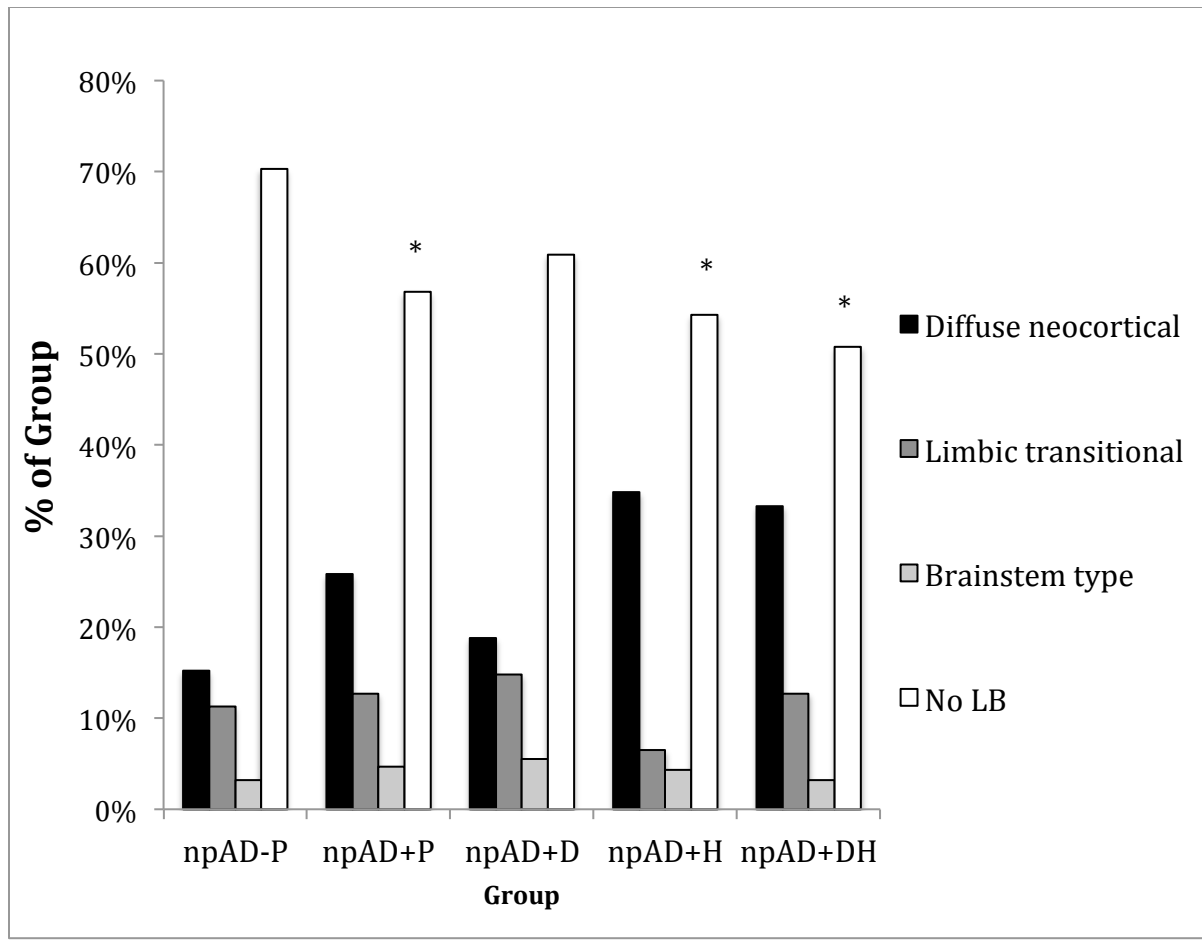


Figure 3.5. Lewy body pathology between neuropathologically confirmed AD patients (npAD), subdivided into those without psychosis (npAD-P) and those with psychosis (npAD+P). The psychotic group was further divided into those with delusions (npAD+D), hallucinations (npAD+H), or both forms of psychosis (npAD+DH). * indicates statistical difference compared to the npAD-P group.

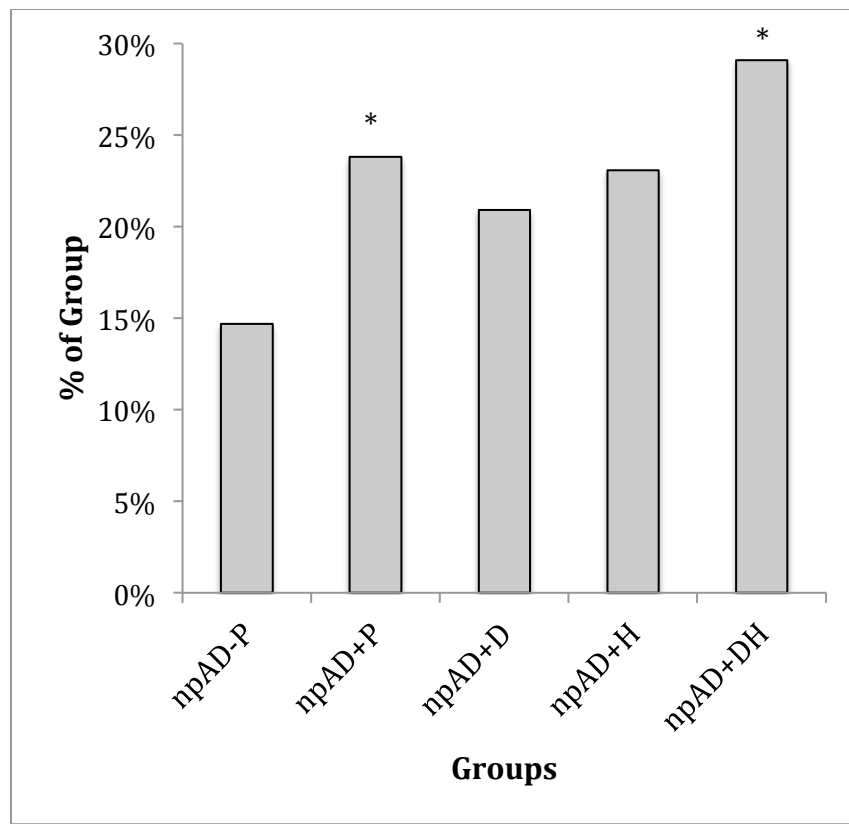


Figure 3.6. Proportion of subjects in each psychosis group with subcortical arteriosclerotic leukoencephalopathy.. * indicates statistical difference compared to the npAD-P group.

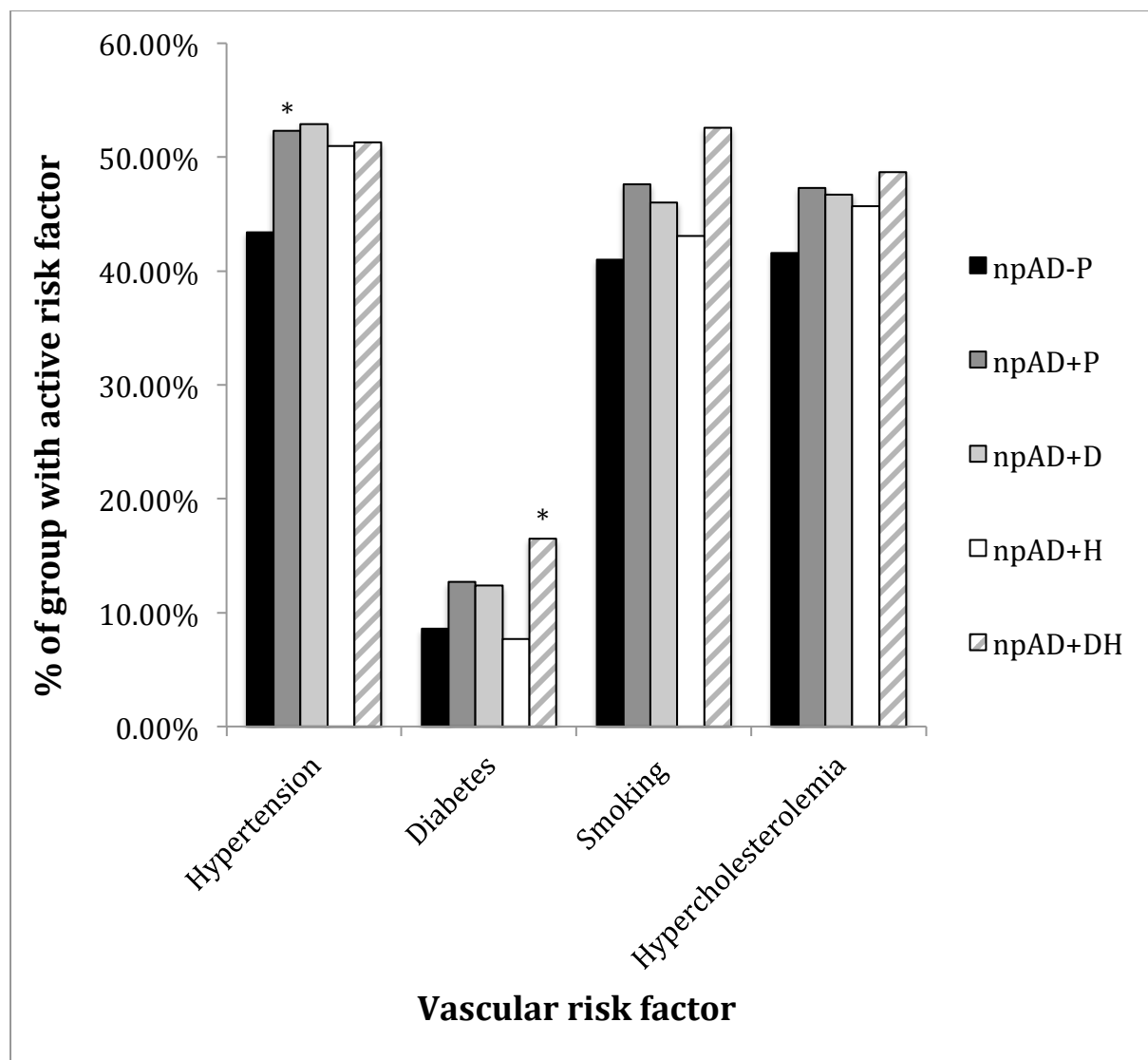


Figure 3.7. Proportion of subjects within each psychotic group with a history of vascular risk factors. Neuropathologically confirmed AD patients (npAD) are subdivided into those without psychosis (npAD-P) and those with psychosis (npAD+P). The psychotic group was further divided into those with delusions (npAD+D), hallucinations (npAD+H), or both forms of psychosis (npAD+DH). * indicates statistical difference compared to the npAD-P group.

3.3 Discussion

The neuropathology section of the current thesis aimed to investigate the neuropathological correlates of delusions and hallucinations. Specifically, if Alzheimer pathology, Lewy body pathology, and/or vascular pathology contributed to the manifestation of psychosis. We made the important distinction between subjects with a clinical versus neuropathological diagnosis of AD, as the latter is the gold standard of definitively determining if a person has AD. A discussion specific to each of the hypothesis outlined in Chapter 2 is detailed below.

3.3.1 Psychosis and the association with markers of AD pathology

In the cAD sample, psychosis was associated with more advanced Alzheimer pathology, including higher Braak and Braak stage, NIA-Reagan scores, CERAD scores and neuritic plaques. Specifically, advanced Braak stage was associated with delusions with or without hallucinations; NIA-Reagan scores correlated with all psychotic groups; CERAD scores correlated with both delusions and hallucinations; and neuritic plaques correlated with delusions only. These findings are consistent with prior studies and support the idea that AD+P may represent a more aggressive form of AD associated with more advanced neuropathology (Farber et al., 2000; Murray et al., 2014a).

3.3.2 Clinical versus neuropathological diagnosis of AD

In contrast to the cAD cohort, the npAD cohort showed no significant associations between any of the measures of Alzheimer pathology and psychotic symptoms, suggesting that the observed findings in the cAD cohort may be driven by misdiagnosis. Evidently, in the cAD

cohort, there was a substantial proportion of subjects, particularly in the AD-D group, who had Braak stages of 0 to III (Figure 3.2) and who had sparse to no neuritic plaques (Figure 3.3). The discrepancy between clinical and neuropathological findings may very well explain the conflicting conclusions in the field to date. The majority of studies reporting a positive (Farber et al., 2000; Koppel et al., 2013; Murray et al., 2014a) or no correlation (Skogseth et al., 2008; Sweet et al., 2000) with Alzheimer pathology relied on clinical diagnosis of AD, which can often be subject to misdiagnosis. A study by Shim et al. found that only 77.67% of patients with a clinical diagnosis of AD exhibited the pathological confirmation of AD (Shim et al., 2013). Therefore, using subjects with neuropathological confirmation of AD is better in evaluating the true pathological correlates of psychosis. Importantly, this was the first study to highlight the difference between clinical and neuropathological AD cohorts with regards to the relationship between AD pathology and psychosis.

However, it should be noted that clinical and neuropathological expressions of AD are not always correlated. Monsell et al. found that some patients who have AD neuropathology are asymptomatic despite neuritic plaque burden, and suggested that neurofibrillary tangles has a larger role in determining the clinical expression of AD (Monsell et al., 2013).

3.3.3 Other pathologies associated with psychosis

Lewy bodies were found to be associated with psychosis in both cAD and npAD cohorts. This is perhaps unsurprising given that Lewy body is a core feature of DLB and PDD, two types of dementias where psychosis is highly prevalent. Moreover, Lewy body pathology has been found to co-occur with AD pathology 50% of the time (Hamilton 2000), further lending support that Lewy body can play a role in mediating psychosis in AD. The finding of an association between Lewy bodies and psychosis is consistent with that of Jacobson et al.

(Jacobson et al., 2014), who found a strong correlation between visual hallucinations and Lewy bodies, both in patients with DLB and clinical AD, and a weak correlation with other markers of AD neuropathology, including neurofibrillary tangles and neuritic plaques. These findings are also consistent with the work of Ballard et al. (Ballard et al., 2004) who found that hallucinations in patients with DLB are inversely related to both neuritic plaques and neurofibrillary tangles, and consequently concluded that psychosis is likely mediated by an alternate disease mechanism from AD pathology.

We found that psychosis was not correlated with specific lesions such as stroke and lacunar infarcts, but both AD+P/AD+DH groups showed a correlation with SAL. Hypertension (in AD+P), and diabetes (in AD+DH) were positively associated with psychotic symptoms as well. Overall, all the vascular risk factors were positively associated with psychosis and its subgroups, although many of them did not reach significance (Figure 3.7). Vascular risk factors increase the likelihood of the development of dementia (Hasnain & Vieweg 2014), and this is consistent with psychosis increasing the likelihood of transitioning from MCI to AD (Peters et al., 2015). Furthermore, psychosis is much more likely to occur in moderate and severe stages of AD, compared to prodromal and early AD. Therefore, the association between psychosis and vascular risk factors, which tend to be more prevalent in older patients, is consistent with the current hypothesis.

Our results suggest that psychotic symptoms in AD patients may be mediated by a vascular mechanism. Therefore, targeting the modifiable aspects, such as managing vascular risk factors (e.g. controlling diabetes and hypertension), may reduce the risk of psychosis.

Previous studies have reported relationships between vascular entities and psychosis in AD, including an association between white matter severity on MRI and delusions (Lee et al., 2006), lacunar infarcts on CT and delusions (Binetti et al., 1993; Binetti et al., 1995),

microinfarcts and arteriosclerosis on pathology with psychosis (Ting et al., 2016), and an association between small vessel disease and delusions (Ogawa et al., 2013). Furthermore, an association between hypertension and the risk of delusions in AD has been reported (Bassiony et al., 2000; Treiber et al., 2008). It has been suggested that vascular burden may disrupt local connections between the frontal lobe and subcortical areas through disruptions of cholinergic transmissions, which may intensify neuropsychiatric symptoms (Kertesz & Clydesdale 1994).

On the other hand, Demichele-Sweet et al. (2011) did not find increased vascular risk factors or vascular lesions in psychotic AD patients (Demichele-Sweet et al., 2011). In the same respect, Steinberg et al. (Steinberg et al., 2014) found that antihypertensive use was only correlated with the affective cluster on the NPI, and not with any other cluster. Bidzan et al. similarly found that vascular factors, as measured by the Hachinski score, were correlated with depression and anxiety, but not with hallucinations or delusions (Bidzan et al., 2014). However, we were the first to correlate vascular changes on pathology, rather than on imaging, with psychotic symptoms. Pathological assessment is more sensitive than imaging in detecting subtle vascular changes.

3.3.4 Clinical and demographic differences

Our samples of cAD and npAD patients with and without psychosis were matched demographically with regards to age and education. Clinical findings that were concordant in both cAD and npAD samples included the finding that AD+P patients were not more functionally impaired at their last clinical visit compared to the AD-P group, contrary to existing literature that suggests psychosis represents a more severe form of AD (Hollingworth et al., 2006; Ropacki & Jeste 2005; Sweet et al., 2010a; Weamer et al., 2009). However, in breaking down symptoms into delusions and hallucinations, we found a distinction between psychosis subtype with regards to disease severity. AD patients with hallucinations, with and without delusions, had more advanced disease (higher CDR

scores) and were more cognitively and functionally impaired (lower MMSE scores and higher FAQs) at the last study visit prior to death compared to non-psychotic patients. Contrary to previous studies (Fischer et al., 2012a), AD+D subjects were not more functionally impaired and, in fact, had significantly lower clinical disease severity at the visit prior to death when compared to AD-P subjects as measured by the MMSE and global CDR. One potential explanation for this finding is that patients with delusions had a longer interval between the last clinical assessments to time of death, so it is possible that the disease progression was less advanced at the last assessment. Another explanation for this finding is that a certain level of cognitive ability is required to form and express a delusion, and that these symptoms remit as cognition declines.

In terms of discordant clinical findings between the cAD and npAD samples, psychotic patients in the cAD sample had a longer duration of illness. This could indicate slower progression and thus less disease severity in patients with AD and psychosis. This would be contrary to some existing literature, which suggests that patients with psychosis undergo a more rapid disease progression (Sweet et al., 2010a). A possible explanation is that perhaps the rate of decline varies at different stages of the AD continuum, with more rapid progression in earlier stages. Currently, the literature is equivocal in regards to associations of AD+P and age of onset and illness duration (Ropacki & Jeste 2005).

In summary, AD patients with psychotic symptoms do not appear to differ demographically or clinically from AD patients without psychosis, but further breakdown of psychotic symptoms showed that patients with hallucinations appear more cognitively and functionally impaired at last visit prior to death, while there is some evidence to suggest that delusions are associated with better cognitive and functional status at last visit prior to death.

3.3.5 Limitations

There are some limitations of the current study. We relied on data obtained from different centers across the United States, so it is possible that there was some variation in the collection of data. We also used many univariate tests in our statistical analysis, which increased the probability of a Type I error. Moreover, we used clinical data obtained from the last study visit, whether or not the patients had active psychotic symptoms at that time, as opposed to looking at the course of symptoms over time. However, most of the subjects exhibited active psychosis at the last visit prior to death. There was also variation in the time between the last clinical visit and time of death, which may have affected the results. Additional, prospective studies will be needed to better define different trajectories of disease in patients with and without psychosis. It is possible that some patients with active psychotic symptoms in fact had delirium, given it may be hard to differentiate the two conditions in advanced dementia. The NPI-Q captures symptoms that have occurred in the previous month, so it is possible that some informant reports may reflect a delirium that had resolved by the time of the study visit. Also, it is possible that clinical differences between patients were not detected secondary to the floor effects of the instruments used (MMSE, CDR, FAQ) given that most patients had advanced dementia. Lastly, concomitant medication should be considered in future studies. It is possible that patients in the non-psychotic control group did not exhibit psychosis because they were treated with antipsychotic medication.

3.4 Chapter 3 Summary

In a large cohort of patients with neuropathological data, we investigated the pathological correlates of psychosis in AD. We found that psychosis was not associated with increased AD pathology burden. Instead, psychosis in AD appeared to be associated with Lewy bodies, subcortical arteriosclerotic leukoencephalopathy, and certain cardiovascular risk factors.

Chapter 4:

Grey matter differences between delusional and non-delusional AD patients

Several studies have investigated the structural brain differences between delusional and non-delusional AD patients, but the results to date remain inconclusive. Initial studies utilizing CT seemed to indicate that reduced grey matter in the right frontal lobe underlies delusions, but more recent studies using MRI, which has greater contrast resolution, implicated a variety of brain regions to be associated with delusions, including many areas of the frontal lobe, temporal lobe, parietal lobe, and even the cerebellum. Furthermore, the limited longitudinal studies have included heterogeneous samples and only one study has looked at the structural brain differences before the manifestation of delusions, but failed to investigate the changes over time.

Chapter 4 of the current study aimed to examine the patterns of grey matter changes associated with the development of delusions by comparing pre- and post-delusional MRI scans. The changes in the delusional cohort were compared to a control group of AD patients who did not develop delusions over the course of follow-up. Furthermore, the baseline differences between pre-symptomatic delusional patients and non-delusional patients, as well as the follow-up differences between post-symptomatic delusional patients and non-delusional patients, were assessed. Understanding the structural brain differences and changes associated with delusions will inform us if abnormalities in specific brain regions may be responsible for delusions.

4.1 Experimental Materials and Methods

4.1.1 Statement of Ethical Approval

Ethical approval for the current study was obtained from the REB at St. Michael's Hospital, Toronto, Canada under REB 13-131 entitled, "Neuroimaging Profiles of Neuropsychiatric Subgroups in Mild Cognitive Impairment and Dementia".

4.1.2 Data source

Clinical data and MRI scans were obtained from the NACC database (Beekly et al., 2007). The current data were collected from 29 ADCs from September 2005 and June 2015. T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) MRI sequences acquired from 1.5 tesla scanners were downloaded from the NACC server.

4.1.3 Eligibility Criteria

Participants must have an AD diagnosis at baseline according to the guidelines by McKhann et al. (McKhann et al., 2011) and have multiple T1 MRI scans that are each within 6 months of a clinical visit. Delusional participants must have an MRI both before and after the clinical onset of their delusions, while non-delusional participants must have MRIs over a similar time span. Patients with frontal-temporal dementia, traumatic brain injury, stroke, Huntington's disease, Down syndrome, CNS neoplasm, and other neurological comorbidities were excluded. The presence of delusions was determined from a score of 1 on the delusional item of the Neuropsychiatric Inventory-Questionnaire (NPI-Q) completed by an informant (Kaufer et al., 2000). Fifty-four patients meeting criteria were identified from the database, including nineteen patients who developed delusions over the course of

follow-up and thirty-five patients who did not developed delusions. None of the patients endorsed hallucinatory symptoms at the scan visits.

4.1.4 MRI analysis

The downloaded MRI images were processed using Statistical Parametric Mapping 8 (SPM8) software (<http://www.fil.ion.ucl.ac.uk/spm>) on Matlab 2010 (R2009a; MathWorks Inc., Natick, MA, USA). Raw Dicom images were converted to NIfTI format using the program dcm2niigui.

4.1.5 VBM analysis

The VBM imaging processing pipeline uses the following steps:

- 1) Spatial normalization: each individual brain scan is transformed to fit onto the same stereotaxic coordinate system (i.e. a template) by averaging the scans. This step corrects for global brain shape differences, but does not aim to match all cortical features exactly
- 2) Tissue segmentation: normalized images are divided into grey matter, white matter, and cerebrospinal fluid
- 3) Modulation: corrects for changes in the brain volume caused by the non-linear spatial normalization in step 1. This step ensures that the total amount of tissue volume is preserved. Unmodulated data compare the concentration or density relative to other tissue

types, which is harder to interpret than modulated data, which compares absolute volume and is thus more useful when measuring atrophy in neurodegenerative diseases

4) Smoothing: increases signal-to-noise ratio by averaging the data point with surrounding area, as well as counteracts some of the data lost from spatial normalization

5) T-tests were used to evaluate regions that are significant different between groups, as well as longitudinally within groups (Mechelli et al., 2005; Senjem et al., 2005).

VBM assess differences across the whole brain, which confers the advantage of not requiring *a priori* assumptions about regions of interest (ROI). Due to the higher number of comparisons, FWE correction, or the more lenient false discovery rate (FDR) correction, are used to reduce the chance of type-1 error. VBM also has the advantage of being a fully automated process, so it is less biased and is less susceptible to human errors.

Intra-subject realignment, bias correction, segmentation into grey matter, white matter, and cerebrospinal fluid, were calculated automatically. The resulting segments were imported for use with DARTEL, which iteratively registered the segments to create an averaged group template. The images were then normalized to Montreal Neurologic Institute (MNI) space to fit the study-specific template. Measurements were not normalized to whole-brain volume. As we were looking at aging and atrophy (i.e. potentially spatially extensive effects in the brain), this step could accidentally “normalize out” the effects of interest, or even lead to paradoxical increases in volume in patients (Peelle et al., 2012). The images were smoothed with an 8mm full-width half maximum isotropic Gaussian kernel. MRI differences for each of the comparisons were computed nonparametrically, using two tailed bootstrapped significance estimates (Efron & Tibshirani 1994). Four

general linear models for two-sample t-test were performed as described below. Multiple comparisons were corrected using FDR at $p < 0.05$. The significant cluster threshold was set at 70 voxels to minimize false positives. MNI coordinates were converted to Talairach space using *GingerALE* software by BrainMap and the anatomical locations for the Talairach coordinates were identified using Talairach Client Atlas. The Mann-Whitney test was used to assess statistical difference in clinical variables because Shapiro-Wilk test of normality was statistically significant. Each voxel has the dimension of 1.5 mm³.

Four VBM comparisons were made in the current VBM analysis (Figure 4.1):

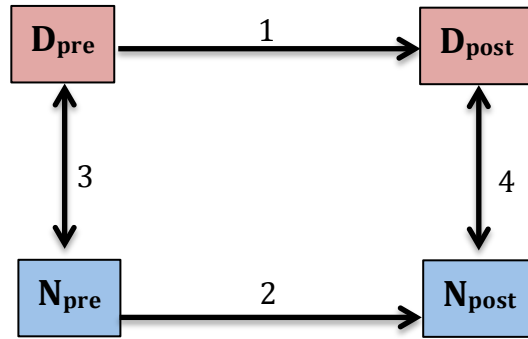


Figure 4.1. Visual depiction of the 4 way VBM comparisons. 1. Comparing the first delusional scan (D_{post}) to the last non-delusional scan (D_{pre}) in the AD+D cohort. 2. Comparing the longitudinal brain changes in the AD-D cohort over a comparable time span as the AD+D cohort. N_{pre} = AD-D baseline scan; N_{post} = AD-D follow-up scan. 3. Baseline differences between the AD+D (D_{pre}) and AD-D (N_{pre}) cohorts. 4. Brain differences at the follow-up scan between AD+D (D_{post}) and AD-D (N_{post}) cohorts.

Comparison 1: AD+D longitudinal

To examine the grey matter changes associated with the development of delusions, the first delusional MRI scan (D_{post}) was compared to the last non-delusional scan (D_{pre}) for patients who developed delusion.

Comparison 2: AD-D longitudinal

Similarly, the longitudinal grey matter changes were assessed in non-delusional patients (N_{pre} and N_{post}) over a similar time span, as indicated by a non-significant statistical difference in time span between the two groups (Table 4.1).

Comparison 3: baseline scan

Baseline grey matter differences between the delusional cohort prior to the onset of delusions (D_{pre}) and the non-delusional cohort (N_{pre}) were assessed.

Comparison 4: follow-up scan

Follow-up grey matter differences between the delusional cohort after the development of delusions (D_{post}) and the non-delusional cohort (N_{post}) were assessed.

4.2 Results

4.2.1 Demographics and clinical characteristics of the subjects

Over the course of follow-up, nineteen patients developed delusions while thirty-five patients did not. Baseline and follow-up demographic data are summarized in Table 4.1. Comparing patients who developed delusions and patients who did not develop delusions, there were no significant differences in age, time between the scans, gender, number of years of education, handedness, or MMSE at the baseline visit, but baseline global CDR was significantly higher in the delusional subset. There were no differences in age, MMSE or global CDR at the follow-up visit between the two cohorts.

Table 4.1. Demographic data for delusional and non-delusional cohorts at the baseline scan and at the follow-up scan

	Delusional subset (n=19)		Non-delusional subset (n=35)		p	
	Pre-delusion Visit (D_{pre})	Post-delusion visit (D_{post})	Baseline visit (N_{pre})	Follow-up visit (N_{post})	Baseline visit	Follow-up visit
Age (mean \pm SD)	78.3 \pm 6.4 (61-91; median 79)	81.2 \pm 5.9 (65-92; median 82)	77.6 \pm 9.2 (50-93; median 79.0)	80.0 \pm 9.4 (51-94; median 82.0)	U=316.5, <i>p</i> =0.904	U=322.5, <i>p</i> =0.993
Change in age between scans	2.7 \pm 1.4 (1-6; median 3)		2.7 \pm 1.9 (0-10; median 2)		U=292.5, <i>p</i> =0.559	
Days between scans	1051.2 \pm 538.1		928.1 \pm 628.5		U=237.0, <i>p</i> =0.184	
Gender	17 F; 2 M		28 F; 7 M		<i>p</i> =0.372	
Education (mean \pm SD)	12.7 \pm 2.9		14.4 \pm 3.2		U=239, <i>p</i> =0.107	
Handedness	17 Right; 1 Left; 1 Ambidextrous		33 Right; 2 Left		<i>p</i> =0.981	
MMSE	23.9 \pm 3.8	19.4 \pm 5.6	25.5 \pm 3.9	21.6 \pm 3.9	U=170.5, <i>p</i> =0.091	U=170, <i>p</i> =0.09
Global CDR	0.69 \pm 0.31	1.19 \pm 0.70	0.44 \pm 0.26	0.94 \pm 0.29	U=122.5, <i>p</i> =0.009*	U=189.5, <i>p</i> =0.599

Note: Values are reported in mean \pm standard deviation (range) unless otherwise stated. P-values are reported for independent samples t-test or Mann-Whitney U. *denotes a significant difference between the two groups.

4.2.2 Results of Comparison 1: AD+D longitudinal

VBM analysis comparing pre- and post-delusional scans in the delusional subset identified 14 significant clusters of locally-reduced grey matter volume over a span of approximately 2.7 years, listed in Table 4.2 and displayed visually in Figure 4.2. Of the 14 clusters of atrophy, 9 (64%) were located on the right hemisphere while 5 (36%) were on the left hemisphere. The superior/middle temporal lobes experienced the greatest atrophy.

Several areas of atrophy in the delusional subset overlapped with the core nodes of the DMN. The atrophic regions within the DMN included the ventral medial prefrontal cortex (medial frontal gyrus, BA10), PCC/retrosplenial cortex (BA30, BA31), IPL (BA39), medial temporal cortex (BA21), dorsomedial prefrontal cortex (medial frontal gyrus, BA10; precentral gyrus, BA9), and the precuneus (BA7) (Table 4.5)

Table 4.2. Suprathreshold voxel clusters differences in the post-delusional scan compared to the pre-delusional scan in 19 AD patients who developed delusions. FDR corrected $p < 0.05$. Clusters are in order of decreasing size.

Cluster No.	MNI coordinate (center of mass)			MNI coordinate (peak)			Cluster size (mm ³)	Anatomical Region/Brodmann Area (BA)	Peak value
	x	y	z	x	y	z			
1	56	-26	-6	56	-14	-2	7392	R Superior/middle temporal gyrus, BA=22, 21	-5.65
2	-58	-32	-30	-58	-32	-18	3696	L middle temporal gyrus, BA=21	-5.38
3	52	-58	4	54	-48	6	3616	R fusiform gyrus, BA=37/R middle temporal gyrus, BA=39	-5.92
4	42	-14	46	42	-8	44	2872	R Precentral gyrus, BA=6	-4.73
5	18	24	58	18	16	60	2072	R superior frontal gyrus, BA=6	-6.67

6	46	-62	40	44	-60	36	1992	R angular gyrus, BA=39/R inferior parietal gyrus BA=40	-5.02
7	32	60	6	34	56	8	1608	R middle frontal gyrus, BA=10	-4.17
8	30	-56	48	30	-52	50	1344	R Precuneus, BA=7/R inferior parietal lobe, BA=39	-4.12
9	-16	-80	24	-12	-72	28	1288	L Precuneus, BA=31, BA=7	-4.24
10	40	28	40	36	24	44	928	R middle frontal gyrus, BA=8	-4.42
11	38	-74	4	40	-76	2	816	R middle occipital gyrus, BA=19	-6.08
12	36	14	28	36	16	26	696	R middle frontal gyrus, BA=9	-4.96
13	-12	34	38	-16	34	44	688	L superior frontal gyrus, B=8	-5.54
14	-16	-64	2	-14	-66	4	672	L Posterior cingulate, BA=30	-4.27

4.2.3 Results of Comparison 2: AD-D longitudinal

The subset of patients who did not develop delusions over the period of observation (September 2005 and June 2015) did not show any significant clusters of atrophy. While there appeared to be some atrophy in the bilateral medial temporal lobes (Figure 4.2), it was not statistically significant.

4.2.4 Results of Comparison 3: baseline scan

At the baseline (pre-delusional) scan, there were 18 significant clusters of grey matter difference between the AD+D and AD-D cohorts. There was an even distribution of clusters between each hemisphere, but all the clusters of lower grey matter volume in the AD+D group were localized to the left hemisphere. The majority of the clusters (14/18) were of higher grey matter in AD+D relative to AD-D, while only 4 clusters were of lower grey matter in AD+D relative to AD-D. The greatest difference was in the right IPL, where the AD+D cohort showed greater grey matter volume.

Table 4.3. Suprathreshold voxel clusters differences in the delusional cohort (n=19) compared to the non-delusional cohort (n=35) at the baseline, pre-symptomatic scan. FDR corrected $p < 0.05$. Clusters are in order of decreasing size.

Cluster No.	MNI coordinate (center of mass)			MNI coordinate (peak)			Cluster size (mm ³)	Anatomical Region/Brodmann Area (BA)	Peak value
	x	y	z	x	y	z			
1	46	-60	42	54	-44	32	5024	R Inferior Parietal Lobule, BA=40/R angular gyrus, BA=39	4.80
2	-10	-76	22	-10	-74	22	2440	L Precuneus, BA=31/L posterior cingulate, BA=31	4.41
3	42	54	0	40	52	0	2424	R inferior frontal gyrus, BA=10/R middle frontal gyrus, BA=10	4.39
4	-6	-8	10	-2	-8	8	1792	L Thalamus, BA=50	-4.63
5	50	-6	32	56	-2	28	1592	R precentral gyrus, BA=6	3.66
6	-14	-82	-22	-14	-84	-22	1544	L occipital lobe, lingual gyrus, BA=18/L cerebellar declive	3.87
7	38	-10	50	40	-16	54	1416	L Precentral gyrus, BA=6	3.76
8	16	58	-10	16	62	-8	1264	R superior frontal gyrus, BA=10/R medial frontal gyrus, BA=10	3.73
9	-64	-42	4	-64	-42	4	1184	L middle temporal lobe, BA=21	3.84
10	44	-72	30	44	-72	32	1168	R angular gyrus, BA=39	3.97
11	62	-4	4	58	-6	4	1080	R superior temporal gyrus, BA=22	4.42
12	20	-76	30	12	-74	28	1048	R Precuneus, BA=31	4.04
13	-22	-10	64	-20	-10	66	912	L middle frontal gyrus, BA=6	-4.39
14	-30	28	-2	-32	26	2	816	L insula, BA=13	-3.70
15	40	8	-16	38	6	-12	792	R insula, BA=13	4.20

16	-24	22	58	-24	22	58	648	L Superior frontal gyrus, BA=8	-3.74
17	-58	-10	22	-56	-10	24	592	L Precentral gyrus, BA=4, BA=6	3.85
18	54	-50	-14	56	-46	-20	584	R inferior temporal gyrus, BA=20/fusiform gyrus, BA=37	3.38

4.2.5 Results of Comparison 4: follow-up scan

At the follow-up (post-delusional) scan, there were 9 significant clusters of grey matter differences between the AD+D and AD-D cohorts. Five of the clusters were localized to the left hemisphere while 4 were localized to the right. The greatest difference was in the frontal lobe, where the AD+D cohort showed significantly lower grey matter volume compared to AD-D. The clusters of higher grey matter in the AD+D group were mainly located posteriorly in the cerebellum and occipital lobe (Table 4.4).

Table 4.4. Suprathreshold voxel clusters differences in the delusional cohort (n=19) compared to the non-delusional cohort (n=35) at the follow-up, post-symptomatic scan. FDR corrected $p < 0.05$. Clusters are in order of decreasing size.

Cluster No.	MNI coordinate (center of mass)			MNI coordinate (peak)			Cluster size (mm ³)	Anatomical Region/Brodmann Area (BA)	Peak value
	x	y	z	x	y	z			
1	-30	6	60	-22	16	58	6144	L middle frontal gyrus, BA=6, L superior frontal gyrus, BA=6, BA=8	-4.01
2	16	14	68	12	16	62	3512	R superior frontal gyrus, BA=6/ R middle frontal gyrus, BA=6/ R superior frontal gyrus, BA=8	-4.34

3	2	-54	-52	2	-48	-52	2832	R cerebellar tonsil	-4.37
4	-26	-90	20	-30	-86	-20	2768	L inferior occipital gyrus, BA=18	4.76
5	30	-40	-58	28	-38	-56	2056	R cerebellar tonsil	5.28
6	-24	-38	-50	-28	-36	-54	1872	L cerebellar tonsil	4.56
7	2	-66	30	2	-66	-28	1784	R cerebellar vermis	4.61
8	-10	-20	66	-14	-20	68	752	L precentral gyrus, BA=6/ L middle frontal gyrus, BA=6	-4.02
9	-12	42	46	-12	44	46	744	L superior frontal gyrus, BA=8	-3.65

Table 4.5. Core regions of the DMN and their respective Brodmann area numbers. The bolded regions are areas that showed atrophy in the AD+D subset following the development of delusions compared to the pre-delusional scan; the italicized regions are areas that were different between the AD+D and AD-D subsets at the baseline, pre-delusional scan; and the underlined regions are areas that were different between the AD+D and AD-D subsets at the follow-up, post-delusional scan.

Network	Location	Brodmann Area
DMN	Ventral medial prefrontal cortex	24, 10 , 32
	Posterior cingulate/retrosplenial cortex	29/ 30 , 23/ 31
	Inferior parietal lobule	39, 40
	Medial temporal cortex	21
	Dorsal medial prefrontal cortex	24, 32, 10, 9
	Hippocampal formation	Hippocampus, EC, PH
	Precuneus	7

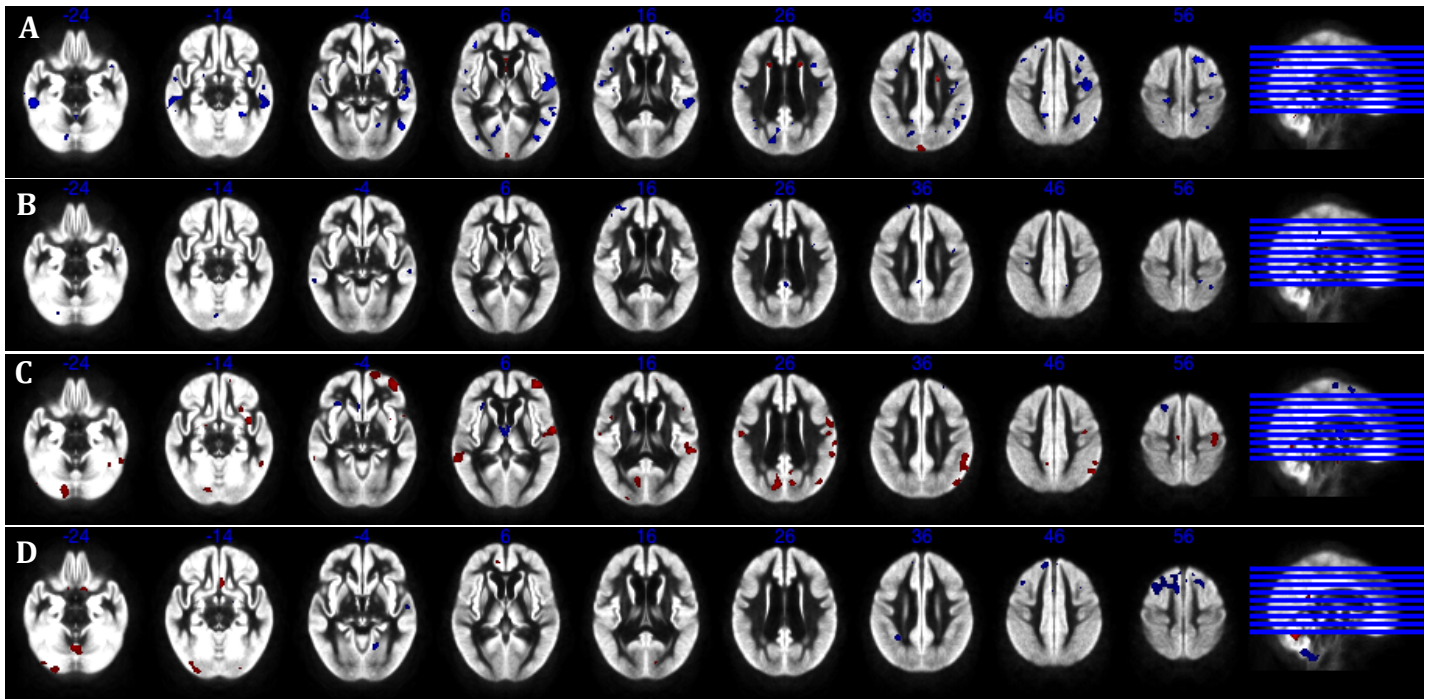


Figure 4.2. VBM results showing clusters of significant grey matter differences between delusional and non-delusional AD patients. Red indicates higher grey matter while blue indicates lower grey matter. **Panel A** shows the longitudinal grey matter differences in the post-delusional scan compared to the baseline pre-delusional scan in the AD+D cohort. **Panel B** shows the longitudinal differences in the follow-up scan compared to the baseline scan in the AD-D cohort. **Panel C** shows the baseline, pre-symptomatic differences in the AD+D cohort compared to AD-D. **Panel D** shows the follow-up, post-symptomatic differences in the AD+D cohort compared to AD-D.

4.2.6. Analysis accounting for disease severity

There was a weak negative correlation between MMSE score and delusional status (two-tailed, $r=-0.16$, $p=0.106$). MMSE and delusional status were independent and did not affect collinearity. Adding MMSE score as a covariate did not significantly change the cluster patterns (data not shown).

4.3 Discussion

The current study used VBM analysis to delineate regions of grey matter differences between delusional and non-delusional AD patients, both prior to, as well as after, the development of delusions. Furthermore, the pattern of grey matter loss from pre- to post-delusions was examined, and the results were compared to that of the non-delusional cohort over a similar time frame.

The results of the study suggest that there were brain differences between the delusional and non-delusional cohorts even before the manifestation of delusions, as well as after the development of delusions, but the patterns of differences at the two scans were markedly different. The results also showed that the delusional cohort exhibited atrophy in brain regions corresponding to the DMN following the development of delusions while the non-delusional cohort did not show any significant atrophy over a similar time frame. This is the first longitudinal study that has implicated the DMN in the development of delusions in AD. Discussions specific to the cross-sectional and longitudinal analyses are detailed below.

4.3.1 Cross-sectional brain differences

The cross-sectional portion of the VBM analysis focused on assessing the differences between the delusional and non-delusional cohorts at the baseline pre-delusional scan, as well as the differences at the follow-up post-delusional scan. The results showed that AD patients with established delusions have significantly less grey matter volume in the bilateral frontal lobes compared to AD patients without delusions. These results are congruent with the hypothesis outlined in Chapter 2, which predicted that patients with delusions would show lower grey matter in the frontal lobe compared to non-delusional

subjects.

The association of delusions with reduced frontal volume supports previous structural imaging studies (Ismail et al., 2012). Reduced volume in the frontal lobes of delusional patients has been the consensus from all the CT studies to date (Burns et al., 1990; Forstl et al., 1991; Geroldi et al., 2002), and has been demonstrated in several MRI studies (Brien et al., 2008; Makovac et al., 2016; Serra et al., 2010; Ting et al., 2015; Whitehead et al., 2012). Although frontal reductions were more frequently reported in the right frontal lobe (Burns et al., 1990; Forstl et al., 1991) than the left (Geroldi et al., 2002) in CT studies, MRI studies remain equivocal with respect to laterality. Within the frontal cortex, MRI studies have localized more specific structures, with the most commonly reported areas being the orbitofrontal cortex (Makovac et al., 2016; Nakaaki et al., 2013b; Rafii et al., 2014; Whitehead et al., 2012) and inferior frontal cortex (Brien et al., 2008; Nakaaki et al., 2013b; Ting et al., 2015). We did not find reduced volume in these particular structures, which could be due to the smaller sample sizes and methodological differences of these previous studies. Nakaaki et al. only investigated pre-delusional brain differences, while Rafii et al. measured atrophy *rates* rather than relative volume. In addition, the sample sizes of the delusional groups from most of these studies were relatively small (average sample size of 16 ± 9.6 , range 5-29) and the delusional cohorts had slight differences. Brien et al. only included misidentification delusions; Serra et al. included misidentification delusions and content-based confabulations; Whitehead et al. only included paranoid delusions and found significant effects only in females; Makovac et al. included delusions as well as hallucinations; and Ting et al. included AD as well as MCI patients. Thus, the small sample sizes and slight differences in the samples could have contributed to the variability in the literature.

Altered metabolism in the frontal lobes has similarly been demonstrated in studies utilizing SPECT and PET (Geroldi et al., 2002; Grady et al., 1990; Lee et al., 2009; Lopez et al., 2001; Matsuoka et al., 2010; Mega et al., 2000; Mentis et al., 1995; Moran et al., 2008; Nakano et

al., 2006; Nomura et al., 2012; Staff et al., 1999; Staff et al., 2000; Sultzer et al., 2003; Sultzer et al., 1995). While hypometabolism has been more frequently reported on the right (Lee et al., 2009; Moran et al., 2008; Nakano et al., 2006; Staff et al., 1999; Staff et al., 2000), hypometabolism has also been reported on the left (Kotrla et al., 1995b; Lopez et al., 2001) or both hemispheres (Sultzer et al., 2003).

Frontal abnormalities are consistent with neuropsychological findings of executive dysfunction in AD patients with delusions and/or hallucinations (Jeste et al., 1992; Nagata et al., 2009; Paulsen et al., 2000a). Executive dysfunction has also consistently been shown to predict psychosis onset (Koppel et al., 2012; Paulsen et al., 2000a; Tsoi et al., 2008). The majority (4/5) of the grey matter clusters that were reduced in the delusional group were located in the prefrontal cortex (PFC), which has long been implicated in higher order cognitive functions. In contrast to simple automatic behaviours that use bottom-up processing, the PFC is responsible for top-down processing to guide goal-oriented behaviour (Miller & Cohen 2001). The PFC is crucial for integrating multimodal inputs and internal states to direct behavioural output, especially when the stimuli are ambiguous which calls for the PFC to select between alternative interpretive options (Miller & Cohen 2001). In this respect, breakdown of areas in the PFC may have an important effect on the development of delusions. It is possible that cues in the environment are misinterpreted, generating illogical conclusions rather than top-down contextually appropriate responses.

In addition to frontal differences, post-delusional AD subjects had higher volume in posterior and cerebellar regions compared to the non-delusional cohort. Although less reported than frontal abnormalities, the correlation between structural changes in the cerebellum and delusions in AD has been previously demonstrated (Fischer et al., 2016). Interestingly, the current delusional cohort exhibited *increased* grey matter, contrary to the findings by Ting et al. However, differences relative to control nonetheless indicates abnormal brain structure, which could contribute to the delusional symptoms. The

cerebellum makes extensive connections to the PFC through the thalamus, as well as to sensory areas and the parietal cortex, suggesting that it performs a wide range of cognitive functions including memory, attention, visual and auditory perceptions (Middleton & Strick 2001; Striener et al., 2015). Cerebellar lesions have been found to cause deficits in visuospatial analysis, working memory, planning, and shifting attention between sensory modalities—cognitive functions subserved by areas of the prefrontal cortex (Middleton & Strick 2001). Moreover, Andreasen et al. (1996)(Andreasen et al., 1996), using PET analysis, found abnormal circuitry in the frontal, subcortical, and cerebellar regions in schizophrenic patients and, in a later study (Andreasen et al., 1998), found that damage to the cerebellum gave rise to psychotic symptoms. It is therefore possible that abnormalities in the prefrontal cortex and cerebellum could lead to delusions.

At the baseline pre-delusional scan, the delusional cohort showed significant differences in grey matter volume compared to the non-delusional cohort. However, contrary to our hypothesis, the majority of the clusters were of greater volume relative to control, distributed across frontal, parietal, occipital, and temporal lobes. Greater grey matter volume was found across both hemispheres, but with slightly more clusters in the right hemisphere. There were also a handful of clusters of lower grey matter in the delusional group, including of the thalamus, middle and superior frontal gyri, and insula, all localized to the left hemisphere.

Many of the clusters of higher grey matter in the delusional cohort—IPL, occipital lobe, temporal gyrus, and precuneus—have been implicated in Capgras syndrome due to their involvement with facial perception (Jedidi et al., 2015). The IPL is part of the dorsal pathway of facial perception, which is required to generate appropriate affective responses to a face (Jedidi et al., 2015). Occipital areas and the superior temporal gyrus, along with the fusiform gyrus, are involved with processing a person's facial features, and the precuneus/PCC and the anterior cingulate cortex are involved with retrieving personal and

emotional information related to the face (Jedidi et al., 2015). Therefore, it is possible that an overactive facial processing system coupled with prefrontal and thalamic degeneration could compromise cognitive control processes involved with sensory interpretations. As a result, individuals may generate inappropriate affective responses to faces and develop delusions, such as of the misidentification type. Alternatively, it has been postulated that increased grey matter density could represent structural damage, in which a compensatory mechanism is initiated to remodel the cortically damaged regions (Li et al., 2012). It is possible that there may be brain reconstruction and compensation at earlier stages, but ultimately atrophies of these areas result in abnormal behavioural symptoms.

Most of the literature investigating structural abnormalities associated with delusions in AD has compared differences *after* delusions have manifested, but brain changes prior to the clinical manifestation of delusions were seldom investigated. In the only study to date looking at pre-delusional differences, Nakaaki et al. found that patients who later develop delusions (n=18) had lower grey matter volumes in the bilateral parahippocampal gyrus, the right orbitofrontal cortex, bilateral inferior frontal gyrus, the anterior cingulate, and the left insula, but *greater* grey matter volumes in the right cerebellum, left lingual gyrus, left inferior temporal gyrus, and left occipital cortex compared to patients who did not develop delusions (n=35) (Nakaaki et al., 2013b). The results of the current study is somewhat consistent with that of Nakaaki et al. by finding regions of both increased and decreased grey matter volumes predating the development of delusions, although the specific regions were not the same. Nakaaki et al. however, only followed subjects for two years, so it is possible that some of the subjects in the non-delusional group later developed delusions. In addition, our study used the last non-delusional scan, so the brain changes may be more pronounced as the subjects were closer to developing delusions.

Interestingly, the areas of higher grey matter in the delusional cohort at the baseline scan

were not significantly different from controls at the post-delusional scan. Many of these areas, including the ventral medial prefrontal cortex (BA10), precuneus (BA31), IPL (BA39), medial temporal cortex (BA21), and the insula (BA6), showed significant longitudinal atrophy. Consequently, the post-delusional brain was predominantly characterized by reduced grey matter compared to control.

4.3.2 Longitudinal brain changes

The longitudinal VBM analysis involved assessing the intra-subject brain changes pre- and post-delusions. Over a span of 2.7 years, the delusional cohort showed atrophy in a variety of brain regions including the right superior and bilateral middle temporal gyri, right superior and right middle frontal gyri, right precentral gyrus, right inferior parietal gyrus, bilateral precuneus, right middle occipital gyrus, and left posterior cingulate. Atrophy of the medial temporal lobe showed the greatest atrophy in the delusional group. As it is one of the hallmarks associated with AD progression, this finding supports the notion that delusional patients undergo a more rapid disease progression. This is consistent with previous literature that report accelerated decline as a risk factor for the development of psychosis (Emanuel et al., 2011; Paulsen et al., 2000b; Peters et al., 2015). In contrast, the non-delusional subset did not show any significant clusters of atrophy in the follow-up scan. The lack of atrophy was unexpected, but it could be due to the relatively conservative FDR correction employed, so that minor atrophy did not reach significance. There appeared to be some atrophy in the bilateral medial temporal lobes, consistent with the typical pattern of neurodegeneration in AD patients (Braak & Braak 1991), but the clusters did not reach significance.

We had hypothesized that there would be predominantly frontal atrophy following the development of delusions, but atrophy was observed in a variety of brain regions in

additional to frontal. Frontal and temporal lobe atrophy and abnormal metabolism have been previously been implicated in delusions in AD (Geroldi et al., 2002; Ismail et al., 2012; Koppel et al., 2014a; Kotrla et al., 1995b; Lopez et al., 2001; Mega et al., 2000; Mentis et al., 1995; Moran et al., 2008; Nomura et al., 2012; Staff et al., 1999; Staff et al., 2000; Sultzer et al., 2003). Previous studies have also reported brain abnormalities of the IPL (Brien et al., 2008; Serra et al., 2010), precuneus (Fischer et al., 2016; Serra et al., 2010), and posterior cingulate (Fischer et al., 2016; Nakaaki et al., 2013b; Rafii et al., 2014).

Although it initially appeared that a collection of individual brain regions showed atrophy following the development of delusions, we noted that many of these regions overlapped with nodes of the DMN, including the medial prefrontal cortex, posterior cingulate, IPL, medial temporal cortex, and the precuneus. Our findings suggest that accelerated atrophy of connected regions that are a part of DMN may be central in the development of delusions, rather than random atrophy in individual regions. Complex cognitive constructs such as psychosis likely go beyond individual brain regions and instead involve connections, or disconnections, between distributed neural circuits. To our knowledge, this is the first neuroanatomical study that has implicated the DMN in the development of delusions in the AD patient population.

4.3.3 Limitations

There were some limitations to our study. Firstly, we did not separate delusions into subtypes. There is evidence to suggest that delusional subtypes, such as persecutory versus misidentification, have separate etiologies and neural correlates (Ismail et al., 2012). Misidentification delusions have been found to occur later in the disease course and have accelerated AD pathology compared to persecutory delusions (Reeves et al., 2012). On the other hand, some have posited that misidentification and persecutory delusions represent

a continuum, where persecutory delusions are milder forms of delusions while misidentification delusions are the more severe form (Reeves et al., 2012). Unfortunately, the delusional data from NACC is determined using the NPI-Q, which does not distinguish between the different types of delusions. Secondly, we did not investigate the effect of other factors on grey matter change, such as medication use (in particular antipsychotic medications), genetics, educational levels, or comorbid neuropsychiatric symptoms. Thirdly, the majority of our sample consisted of females, which could have introduced a gender bias. The prevalence of AD, as well as psychosis in AD, is higher among females (Hirono et al., 1999; Ikeda et al., 2003), which likely influenced the sample enrolment. There have been studies reporting gender differences. Whitehead et al. (Whitehead et al., 2012) previously found reduced cortical thickness in the left medial orbitofrontal and left superior temporal regions in female AD patients with paranoid delusions, but the effect was not found in male patients. Therefore, grey matter atrophy associated with delusions could affect the genders differently. Separating our analysis by gender wasn't feasible due to low sample size so we could not make any conclusions regarding gender. However, the delusional and non-delusional groups were comparable in the proportion of females.

4.4 Chapter 4 Summary

In Chapter 4 of the current thesis, we investigated the grey matter abnormalities associated with delusions, both cross-sectionally and longitudinally. Patients who developed delusions showed increased atrophy, with many areas of atrophy overlapping with areas of the DMN. In contrast, the cohort of subjects who did not develop delusions did not show significant atrophy over a similar time frame. Furthermore, there appear to be brain differences both prior to as well as after the clinical onset of delusions. The findings support that delusional and non-delusional AD patients have distinct structural neural correlates that may be related to functional networks.

Chapter 5:

Resting-State Functional Connectivity

While our initial understanding of the physiology of the brain and its functions were predicated on the modular paradigm, there is a shift in focus to investigate the macro-scale functional architecture. There is converging evidence to suggest that disruptions to intrinsic functional networks may be a key mechanism underlying many neuropsychiatric disorders. Altered resting-state connectivity has been observed in various populations, including AD, schizophrenia, bipolar, depression, and autism (Buckner et al., 2008). Altered resting-state connectivity has also been implicated in neuropsychiatric symptoms within AD, such as depression and anxiety. To date, the only study investigating the functional connectivity of psychosis in AD utilized a very heterogeneous sample, consisting of delusions (n=2), hallucinations (n=2), and night-time behaviours (n=6) (Balthazar et al., 2014). Therefore there is a gap in the literature in elucidating the functional resting-state architecture specific to delusions in AD. In Chapter 4, we found that many areas of the DMN exhibited structural atrophy following the development of delusions. In Chapter 5, we will further examine the relationship between delusions and functional networks using functional resting-state analysis. Understanding how the functional networks are compromised in delusions can pave the way for novel therapies to target these specific networks.

5.1 Experimental Materials and Methods

5.1.1 Statement of Ethical Approval

Ethical approval for the current study was obtained from the REB at St. Michael's Hospital, Toronto Canada under REB 15-085 entitled, "The Neural Correlates of Delusions in Patients with Cognitive Impairment".

5.1.2 Study Participants

Thirty (30) AD patients were recruited from the St. Michael's Hospital and the Centre for Addiction and Mental Health (CAMH) Memory Disorders Clinics, including fifteen (15) patients with delusions (AD+D) and fifteen (15) controls without delusions (AD-D). A PRISMA diagram indicating how many patients were excluded, and the reason for exclusion, is shown in Figure 5.1.

Inclusion criteria

- (1) Diagnosis of Alzheimer's disease
- (2) Speaks English
- (3) Has a caregiver who can accompany the participant to the research visit

All patients were diagnosed with AD by a geriatric psychiatrist in the Memory Disorders Clinics, according to the NIA-AA criteria for AD (McKhann et al., 2011). The NIA-AA criteria for probable AD include the following criteria: 1) dementia established by examination and objective testing, 2) insidious onset, 3) progressive worsening of memory and other cognitive functions, 4) the initial and most prominent cognitive deficit is amnesic or non-amnesic (language, visuospatial, or executive). A diagnosis of probable AD should not be given if there is significant cardiovascular disease, prominent features of dementia with Lewy bodies, frontotemporal dementia, semantic variant or agrammatic variant primary progressive aphasia, evidence for a neurological disease, medical co-morbidity or medication use that may have negatively impacted cognition. At the Memory Disorders Clinics, a comprehensive medical history, neuropsychological testing (including the Mini-Mental State Exam (MMSE) (Folstein et al., 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), and the Behavioural Neurological Assessment (BNA) (Darvesh et al., 2005)), laboratory blood work to rule out reversible causes of cognitive impairment, and clinical imaging (MRI or CT, SPECT) were used in the assessment.

Exclusion criteria

The following represent exclusion criteria for the participants:

- (1) History of severe neurological illnesses (e.g. traumatic brain injury, brain tumour, Parkinson's disease, stroke, multiple sclerosis, epilepsy, etc.)
- (2) History of severe psychiatric diagnosis (e.g. schizophrenia, bipolar, uncontrolled depression or anxiety, etc.)
- (3) Presence of serious sensory or motor impairment
- (4) History of substance abuse or dependence
- (5) Diagnosis of a learning disability
- (6) Not MRI compatible
- (7) Presence of hallucinations for the non-delusional control group

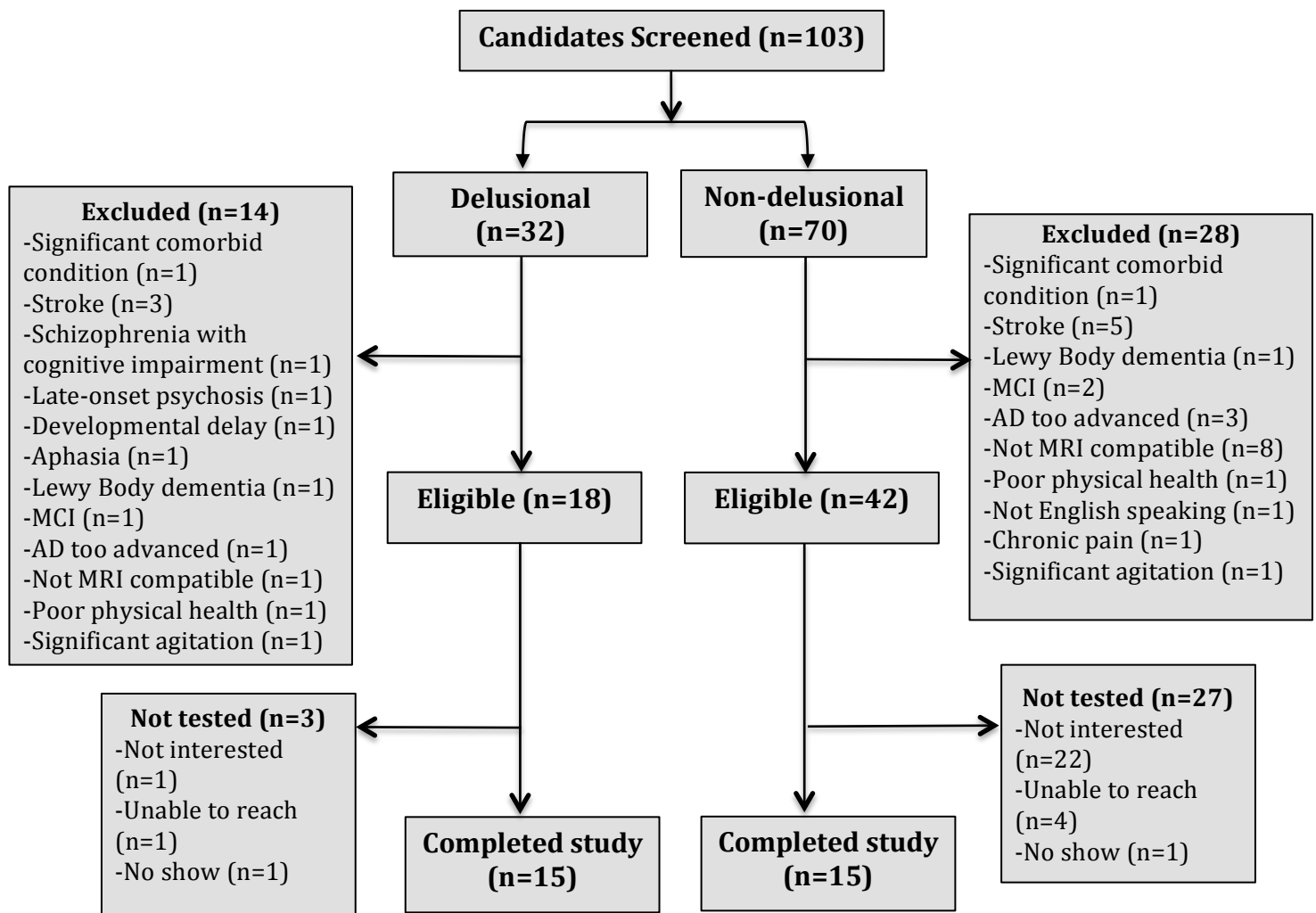


Figure 5.1. PRISMA diagram showing how many patients were excluded and the reasons for exclusion

5.1.3 Data acquisition

Chapter 5 of the current study aimed to test the hypothesis that delusional patients will display abnormal resting-state connectivity in large-scale networks. Each potential participant was pre-screened over the phone or in person to ensure that inclusion and exclusion criteria were met. All study protocol was completed in one research visit, lasting approximately 1.5 hours. Each participant completed the MRI scanning session lasting

approximately 40 minutes. After the scan, the participant changed back to their clothing and completed a MoCA immediately after. Therefore, the time between imaging and assessment is the same across all subjects, which is approximately 5-10 minutes. The caregiver who accompanied the patient to the research visit completed the questionnaires in a clinical-interview setting with the research assistant during the MRI scan.

5.1.3.1 MRI acquisition protocol

Participants were imaged at St. Michael's Hospital using a research-dedicated 3.0 Tesla MRI system (Magnetom Syngo Skyra, Siemens, Erlangen, Germany) with a standard 20-channel head receiver coil. All MRI sequences were conducted by a certified MRI technologist. Structural brain imaging included a T1-weighted MPRAGE sequence (echo time (TE) = 2.54 ms, TR = 2000 ms, 176 slices, thickness = 1.0 mm, gap = 0 mm, field of view (FOV) = 256 mm, 1.0 x 1.0 x 1.0 voxels). Rs-fMRI (awake, eyes closed) lasting approximately 8 minutes were evaluated using T2-weighted fast echo-planar images (EPI; echo time (TE) = 30.0 ms, TR = 2000 ms, 32 slices, thickness = 4.0 mm, gap = 0.5 mm, field of view (FOV) = 200 mm, 3.1 x 3.1 x 4.0 voxels). In addition, arterial spin labeling (ASL) and DTI images were taken to be utilized by a separate study.

5.1.3.2 Clinical Data, Cognitive Testing, Functional Questionnaires

Clinical data, including the diagnosis, past medical history, and imaging results were obtained from the electronic medical record system Soarian Clinicals (version 4.00 SP06). Questionnaires that were administered to the accompanying caregiver included a demographic questionnaire, the Neuropsychiatric Inventory Questionnaire (NPI), Older Americans Resources and Services (OARS), and the Disability Assessment for Dementia (DAD). The cognitive test used immediately after the MRI scan was the MoCA. The cognitive

and functional measures were conducted to verify that the two cohorts were comparable in disease severity.

Demographic Questionnaire

All subjects were asked for their demographic information, including age, handedness, years of education, and occupation. Also, any family history of dementia, a list of medication, and past medical history, including hypertension, diabetes, coronary artery disease, dyslipidemia, atrial fibrillation, smoking, and depression, were inquired.

Neuropsychiatric Inventory Questionnaire (Cummings et al., 1994)

For all patients participating in the study, delusional status was assessed using the Neuropsychiatric Inventory Questionnaire (See section 1.1.3.2).

Older Americans Resources and Services (OARS) (George & Fillenbaum 1985)

The OARS measures ADL, which includes the basic functions (BADL) as well as instrumental functions (IADL). The OARS has been used since 1985 to assess the functional ability of older adults in a variety of settings. The seven BADL items on the OARS include eating, dressing and undressing, grooming, walking, getting in and out of bed, bathing, continence. The seven IADL items on the OARS include using the telephone, travel, shopping, meal preparation, housework, taking medicine, and management of finances. The OARS can be administered to either the patient or an informant, but the latter was used in the current study. Informants were asked if the patient could perform each of the activities without any help at all (2 points), some help (1 point), or if they were completely unable to perform the activity (0 points). The three scores generated from the OARS include a total score on all 14 items (range 0-28), a BADL score on the 7 BADL items (range 0-14), and an IADL score on the 7 IADL items (range 0-14).

Disability Assessment for Dementia (DAD) (Gelinas et al., 1999)

The DAD, developed by Gauthier and G  linas, is a measure of functional ability in patients with dementia. It is completed through an interview with the caregiver/informant to evaluate BADLs and IADLs. The DAD comprises of 40 items divided into the domains of hygiene, dressing, undressing, continence, eating, meal preparation, telephoning, going out, finances, taking medication, and leisure and housework. Each item on the scale is categorized as an initiation item, a planning and organization item, or as a performance item. Of the 40 items, 13 are initiation items (e.g. undertake to wash himself/herself), 10 are planning and organization items (e.g. prepare the water, towels, and soap for washing), and 17 are performance items (e.g. wash and dry completely all parts of his/her body safely). Each item is given a score of 1 if it is undertaken in the last two weeks without help or reminder, or a score of 0 if it was not undertaken. The DAD has been shown to have excellent inter-rater reliability and test-retest reliability (McIntyre 1994). Criterion validity has also been established between the DAD and the Global Deterioration Scale (GDS) (Reisberg et al., 1988) and the MMSE (Folstein et al., 1975).

Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005)

The MoCA, developed by Nasreddine and colleagues (2005), is one of the most widely used cognitive tests used to screen for global cognitive impairments. The test has a total score of 30, and a score of ≥ 26 suggests normal cognition while a score of < 26 suggests cognitive impairment that may be related to AD, mild cognitive impairment, or other types of dementias. The eight cognitive domains assessed are: visuospatial/executive (scored out of 5), naming (scored out of 3), attention (scored out of 6), language (scored out of 3), abstraction (scored out of 2), delayed memory recall (scored out of 5), and orientation (scored out of 6). If the individual has twelve or less years of education, an additional point is added to the total score.

The MoCA has high validity and specificity, and has much higher sensitivity than the MMSE

in detecting cognitive impairment. The MoCA has been used in both clinical and research settings and in a variety of patient populations (AD, mild cognitive impairment, frontotemporal dementia, vascular dementia, vascular cognitive impairment, stroke) (Freitas et al., 2014; Goldstein et al., 2014; Kaya et al., 2014; Lam et al., 2013; Schweizer et al., 2012; Smith et al., 2007). The MoCA is an important tool recommended by the Canadian Consensus Conference for the Diagnosis and Treatment of Dementia Guidelines for Alzheimer's disease (Canadian Consensus on Diagnosis and Treatment of Dementia Working Group 2007).

5.1.4 Data Analysis

5.1.4.1 Cognitive and Questionnaire Data Analysis

The MoCA, NPI, DAD, and OARS were scored according to published methods described above. Statistical analyses of all data were analyzed using SPSS version 21 (IBM 2012). Normality of continuous data was assessed using the Shapiro-Wilk test due to the relatively smaller sample size. If the variable was normally distributed, then an independent samples t-test was used to evaluate the pairwise difference between delusional patients and non-delusional controls. If the Shapiro-Wilk test was significant, indicating a non-normal distribution, then the Mann-Whitney U test was used. The chi-square (χ^2) test of independence was used to statistically assess categorical variables.

Significance level was set at $p < 0.05$. As demographic and cognitive data were primarily used to assess if the two cohorts were clinically comparable, multiple corrections were not used for clinical assessments. As the imaging was the main outcome, fMRI analysis was corrected using FDR.

5.1.4.2. Resting-state fMRI data analysis

There are several methods for analyzing resting-state data, all of which use temporally coherent fMRI time-courses to show functionally related activity. Two of the most common approaches are seed-based analysis and independent component analysis. **Seed-based** analysis involves choosing an *a priori* ROI and subsequently constructing a map of other voxels in the brain that correlate in average BOLD signal with the voxels in the ROI (Biswal et al., 1995; Biswal et al., 1997; Cordes et al., 2002; Cordes et al., 2000; Lowe et al., 1998) (N.B. Voxels are the basic volumetric building units of the brain. In a 1.5 Tesla or 3.0 Tesla MRI, each voxel of the brain has a dimension of $2 \times 2 \times 2 \text{ mm}^3$, which contains around a million neurons). The temporal coherence can be between the seed region and another node (connectivity between A and B), or can be between the seed region and regions within the same network (connectivity of network A). Seed-based analysis typically requires a threshold of a number of voxels that are correlated to reach significance. The other common method of analyzing functional connectivity is **independent component analysis (ICA)** (Calhoun et al., 2001; Esposito et al., 2005; McKeown et al., 1998). ICA is a powerful technique that separates multivariate signals into independent signals. ICA can be used to identify distinct RSNs. Compared to seed-based analysis, ICA does not require *a priori* ROI, and so it is more data-driven and exploratory. In addition, ICA allows for better removal of noise components (motion, scanner drift, etc.). Despite the differences, the two methods of analyses generate significantly similar results in healthy subjects (Rosazza et al., 2012). Both methods also have well-established validity for analyzing resting-state functional connectivity data, both between and within subject groups. Studies have shown that RSNs have excellent test-retest reproducibility (Biswal et al., 2010; Shehzad et al., 2009) and inter-subject consistency (Damoiseaux et al., 2006; Shehzad et al., 2009).

In the current analysis, the following steps were taken to analyze rs-fMRI data:

The format of the image files was converted from Digital Imaging and Communications in Medicine (DICOM) to Neuroimaging Informatics Technology Initiative (NIfTI) using the software MRIconvert. Next, the images were preprocessed with a standard fixed set of preprocessing steps using the PReprocessing Optimization TOolkit (PRONTO) software (Churchill et al., 2012a; Churchill et al., 2012b). PRONTO optimizes the BOLD fMRI pipeline specific to the dataset, and has been shown to significantly improve the signal-to-noise ratio, reliability of activation, and sensitivity to brain-behaviour correlations (Churchill et al., 2012a; Churchill et al., 2012b). The pipeline is analysis-driven, meaning it uses Prediction and Reproducibility metrics to select the pipeline that gives the output with the highest quality. For the current data, the pre-processing steps included rigid-body motion correction with optimal reference for volume section, adaptive correction of physiological noise and residual motion artefact, along with spatial smoothing and high-pass filter. Tools from Analysis of Functional Neuroimaging (AFNI) (Cox 1996) and FMRIB Software Library (FSL) were used in the preprocessing of resting-state data.

An in-house script ran on Matlab was used. A pipeline file specifying the name and the location of the files to be processed, the name and location of the processed output files, and the number of images to be dropped at the start and end of the scan, was created. The first two and last two volumes of the time series were discarded so that the rest of the volumes are at a steady state magnetization. Images were smoothed with a 6mm full-width at half maximum (FWHM) Gaussian filter to improve signal-to-noise ratio. After preprocessing, the functional scans were aligned to the structural T1 scans, which were registered to the MNI152 standard space using affine linear registration (Jenkinson et al., 2002).

Group analysis was based on the dual-regression, group ICA approaches developed by the FSL group from Oxford, UK that were previously used in the literature. Principal component analysis (PCA) on individual subjects was performed and spatial ICA was

applied to the concatenated subject principal components to identify group-level independent components. The independent component depicting the DMN was identified based on the regions described in the literature (Damoiseaux et al., 2008; Greicius et al., 2004), and the component was selected for between-group analyses. The corresponding individual subject DMN maps was generated by regressing the group independent component pattern onto subject data, and using the corresponding time course as a temporal regressor. To identify the differences in connectivity between the delusional and non-delusional patients, a two-samples t-test was used, with FDR correction.

5.1.4.2. Sample size and power calculations

Sample size calculation is based on following equation (Statistical Consulting Group 2014):

$$n_x = \frac{(r + 1)\sigma^2(Z_\beta + \frac{Z_\alpha}{2})^2}{r(\mu_y - \mu_x)^2}$$

$$= 35.6$$

For regions showing significant DMN activity ($p < 0.005$, 1-sample test), to detect a reliable between-group effect at 0.80 to 0.90 power requires a sample range of 36-44.

5.2 Results

5.2.1 Clinical and demographic data

There were no significant differences in age, education, sex, handedness, or MoCA scores between delusional and non-delusional participants (Table 5.1). Psychoactive medication in each cohort is listed in Table 5.2. None of the subjects were on antipsychotic medication, and the cohorts were comparable in the proportion of subjects taking cognitive enhancers and anti-depressants. There were no significant differences on the OARS or DAD, or their

subcomponents, between delusional and non-delusional participants (Table 5.1). The delusional cohort had significantly higher total NPI frequency ($p=0.033$), total NPI severity ($p=0.013$), and total caregiver distress ($p=0.050$) compared to non-delusional controls (Table 5.1). Assessing the domains of the NPI, delusional patients had significantly higher co-occurrence of hallucinations ($p=0.032$), depression ($p=0.02$), and irritability ($p=0.046$) compared to the non-delusional group (Figure 5.2). There were no statistical differences in history of cardiovascular risk factors or depression between delusional and non-delusional patients (Table 5.3).

Table 5.1. Clinical and demographic data of delusional and non-delusional participants

	Non-delusional (n=15)	Delusional (n=15)	p-value
Age	79.6 ± 6.7 (69-91)	76.9 ± 7.0 (63-88)	0.298
Education	13.7 ± 3.6 (3-17)	15.2 ± 3.3 (8-21)	0.345
Sex	6 males (40.0%) 9 females (60.0%)	5 males (33.3%) 10 females (66.7%)	0.705
Hand	14 right handed (93.3%) 1 ambidextrous (6.7%)	14 right handed (93.3%) 1 ambidextrous (6.7%)	1.000
MoCA	16.7 ± 5.6 (3-23)	13.9 ± 5.4 (4-22)	0.185
OARS	23.7 ± 3.9 (15-28)	21.7 ± 6.0 (7-28)	0.305
OARS (BADL)	13.8 ± 0.4 (13-14)	13.1 ± 1.9 (7-14)	0.624
OARS (IADL)	9.9 ± 3.6 (2-14)	8.6 ± 4.5 (0-14)	0.398
DAD (initiating)	0.78 ± 0.24 (0.25-1)	0.64 ± 0.27 (0.08-1)	0.146

DAD (planning)	0.75 ± 0.27 (0.2-1)	0.57 ± 0.31 (0-1)	0.146
DAD (performance)	0.77 ± 0.26 (0.18-1)	0.63 ± 0.27 (0.18-1)	0.146
NPI total frequency	5.5 ± 5.9 (0-18)	11.1 ± ±8.5 (2-29)	0.033*
NPI total severity	3.1 ± 3.3 (0-10)	7.8 ± 6.2 (1-21)	0.013*
NPI total distress	3.5 ± 4.2 (0-15)	8.9 ± 8.9 (0-26)	0.050*

Note: Values are reported in mean ± standard deviation (range) unless otherwise stated. P-values are reported for independent samples t-test or Mann-Whitney U. *denotes a significant difference between the two groups.

Table 5.2. Psychoactive medication taken by subjects

Psychoactive Medication	Non-delusional (n=15)	Delusional (n=15)	p-value
Antipsychotic	0 (0.0%)	0 (0.0%)	
Cognitive Enhancer	6 (40.0%)	6 (40.0%)	
Depression	2 (13.3%)	3 (20.0%)	$\chi^2=0.24$; $p=0.624$

Note: Values are reported in count (percentage). P-values are reported for chi-square tests between the two cohorts. *denotes a significant difference between the two groups.

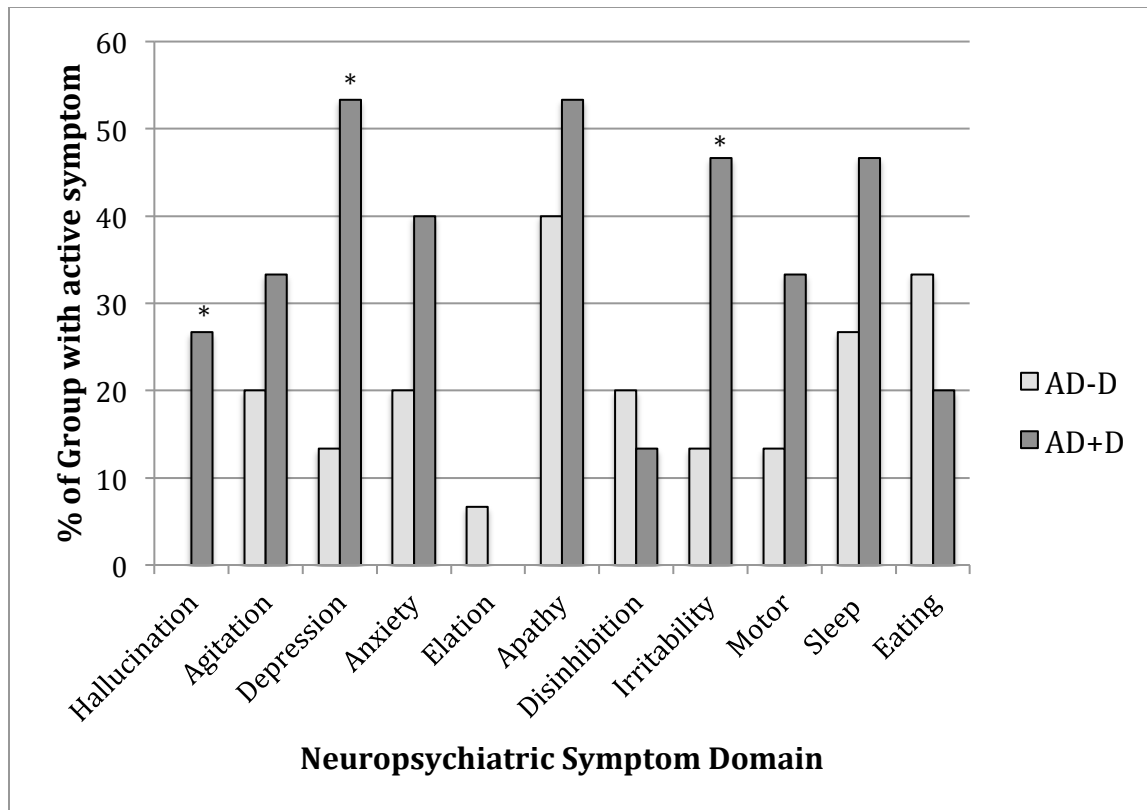


Figure 5.2. The prevalence of each neuropsychiatric symptom domain on the NPI for delusional (n=15) and non-delusional (n=15) groups. Hallucination, depression, and irritability were significantly more prevalent in the delusional group. *denotes a significant difference between the two groups.

Table 5.3. The prevalence of cardiovascular risk factors in delusional and non-delusional groups

Medical history	Non-delusional (n=15)	Delusional (n=15)	p-value
Hypertension N (%)	10 (66.7%)	6 (40.0%)	.143
Diabetes	3 (20.0%)	4 (26.7%)	.666
Coronary artery disease	0 (0.0%)	1 (6.7%)	.309
Dyslipidemia	8 (53.3%)	5 (33.3%)	.269
Smoke	9 (60.0%)	5 (33.3%)	.143
Depression	3 (20.0%)	8 (53.3%)	.058

The types of delusions exhibited by the delusional cohort are listed in Table 5.4. Persecutory delusions were experienced by 73.3% of the delusional subjects, while misidentification delusions were experienced by 53.3% of the delusional subjects. Four of fifteen subjects (26.7%) experienced both persecutory and misidentification delusions. Delusion of theft was the most frequent type of persecutory delusion (53.3%), followed by delusion of harm/abandonment (33.3%), and then delusion of jealousy/infidelity (6.7%). Phantom boarder (33.3%) and the belief that the house is not one's home (33.3%) were the most frequent types of misidentification delusion, followed by familiar person/Capgras syndrome (13.3%) and nurturing delusion (believing a dead family member is still alive; 13.3%). Other types of delusions that were endorsed included delusions of grandeur, the belief that messages were being transmitted through the walls, the belief that the subject was receiving messages from the president with secret missions, and the belief that the

subject had to go to work. On average, each delusional subject experienced 2.4 types of delusions.

Table 5.4. Breakdown of delusion subtypes in the AD+D cohort, including the number of subjects and the subject IDs with that particular delusion.

Delusion type	Number of subjects (% of delusional cohort)	Delusional participant's ID
Persecutory	11 (73.3%)	1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 15
Theft	8 (53.3%)	1, 3, 6, 7, 8, 11, 12, 15
Harm/abandon	5 (33.3%)	1, 2, 4, 5, 7
Jealousy/infidelity	1 (6.7%)	3
Misidentification	8 (53.3%)	4, 7, 9, 10, 11, 12, 13, 14
Familiar person	2 (13.3%)	10, 14
Capgras	2 (13.3%)	10, 14
Phantom boarder	5 (33.3%)	4, 7, 9, 10, 12
Mirror delusion	1 (6.7%)	12
Nurturing	2 (13.3%)	11, 13
TV	1 (6.7%)	9
House not home	5 (33.3%)	3, 9, 10, 11, 12
Other delusions	4 (26.7%)	2 (they're special/chosen), 5 (message transmitting through walls), 9 (receiving letters from president), 10 (has to go to work)

5.2.2 Resting-state fMRI results

We extracted the third component that accounted for the greatest group-level variance because it is largely consistent with the DMN based on prior literature (Damoiseaux et al., 2008; Greicius et al., 2004). This component contained BOLD fMRI signals in the bilateral precuneus, medial prefrontal cortex, bilateral medial temporal lobes, and bilateral IPLs including the angular gyrus (Figure 5.3). Post-hoc analysis of this component showed that patients with delusions had significantly weaker coherence between the left IPL (including the angular gyrus) with the overall DMN (FDR corrected) (Figure 5.4).

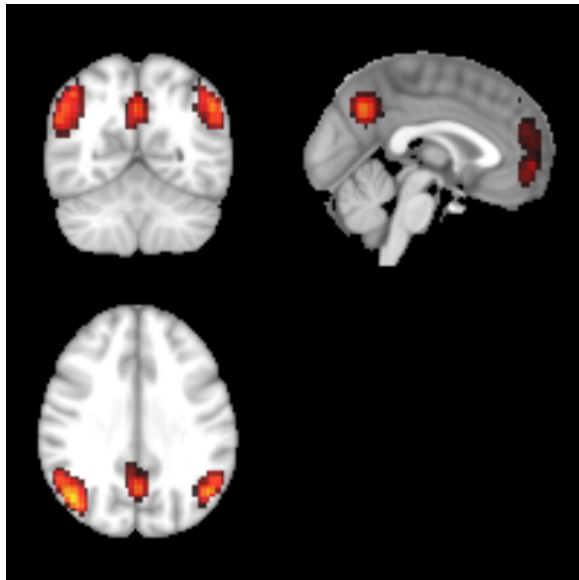


Figure 5.3. Network identified by PCA as the third network accounting for the largest variability in subjects. This network resembles the DMN, encompassing the bilateral precuneus, medial prefrontal cortex, bilateral medial temporal lobes, and bilateral IPLs including the angular gyrus

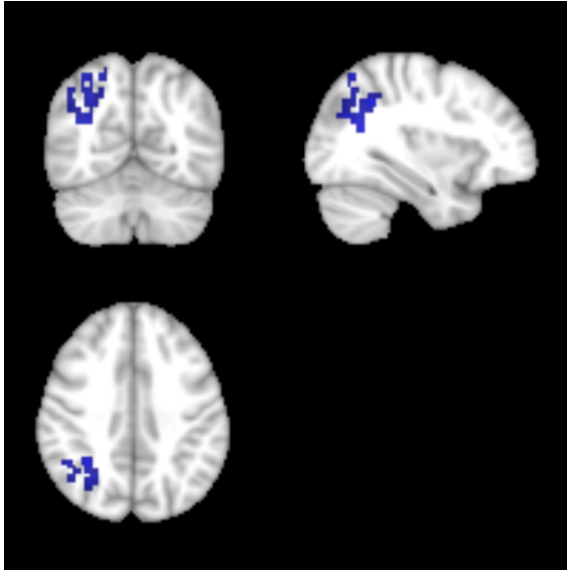


Figure 5.4. Post-hoc analysis of component 3 showing significantly decreased connectivity of the IPL with the overall network.

Additionally, there was an anterior, frontal component that was also reliably generated from PCA, consisting of the superior frontal, middle cingulate, and precentral regions (Figure 5.4). We decided to further explore this network given the strong association between frontal regions and psychosis in the literature. However, there were no significant connectivity differences in this network between the delusional and non-delusional patients.

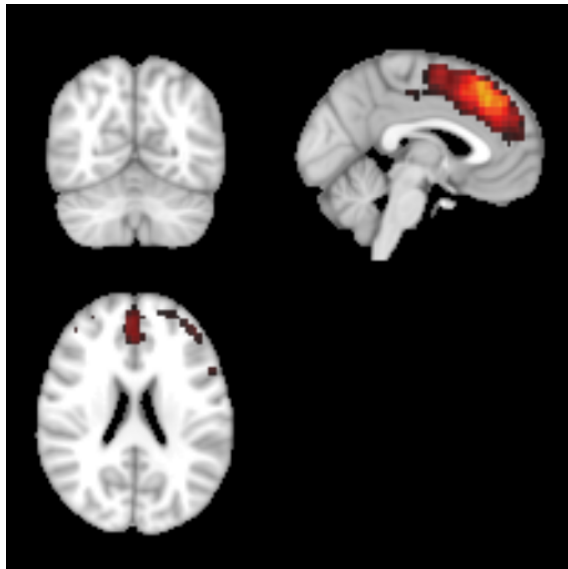


Figure 5.5. An anterior network identified by PCA as the second network accounting for the largest variability in subjects. This network encompassed the superior frontal, middle cingulate, and precentral regions.

A second bootstrap generalized linear model was performed that included MoCA score as a covariate. There was a small reduction (17.6%) in the number of voxels that were significantly different between the cohorts, but the results were not fundamentally changed, with the IPL remaining significant. The reduction in significance was expected due to lower power when additional variables are included into the model.

5.3 Discussion

Building on our findings from Chapter 4, which found accelerated atrophy of regions of the DMN following the development of delusions, Chapter 5 aimed to further investigate resting-state connectivity differences between delusional and non-delusional AD patients.

The delusional and non-delusional patients were comparable in age, education, sex, handedness, cognitive status, and functional status. The delusional group had higher co-occurrence of other neuropsychiatric symptoms (in particular hallucination, depression, and irritability), had higher frequency of neuropsychiatric symptoms, and had higher caregiver distress than the non-delusional group. These findings are concordant with the previous studies, which report higher rates of other neurobehavioural symptoms in psychotic AD patients, such as depression (D'Onofrio et al., 2016; Lyketsos et al., 2001; Sweet et al., 2010b), agitation (Bruen et al., 2008; D'Onofrio et al., 2016; Gilley et al., 1991), and aggression (D'Onofrio et al., 2016; Deutsch et al., 1991; Forstl et al., 1993b; Gilley et al., 1997; Sweet et al., 2001). It is also consistent with previous studies that similarly found higher caregiver burden and distress in association with delusions (Fischer et al., 2012b; Gauthier et al., 2010; Kaufer et al., 1998; Lee et al., 2013a).

Using rs-fMRI, we showed that delusional AD patients exhibited significant reduction in the intrinsic connectivity of the DMN compared to non-delusional controls. This was consistent with our hypothesis, which predicted that delusions would be associated with decreased DMN connectivity. Specifically, we demonstrated that delusions were associated with decreased integration of the left IPL with the overall DMN. No differences were found in the anterior frontal network in association with delusions.

To our knowledge this is the first study to investigate the resting-state connectivity of AD patients with delusions. Alterations in functional networks, particularly the DMN, are becoming increasingly recognized as being relevant in pathophysiology. The DMN is believed to be activated when a person is engaged in internally focused tasks such as self-monitoring, thinking about the self and others, autobiographical memory retrieval, mind-wandering, and envisioning the future (Buckner et al., 2008; Cabeza et al., 2002; Fair et al., 2008; Greicius et al., 2004; Gusnard et al., 2001; Leech et al., 2011; Mason et al., 2007). The DMN is also involved in tasks of social cognition, including inferring other's emotional

statuses, beliefs, and intentions, judging the motives of others' behaviour, and in empathy towards others (Buckner & Carroll 2007; Grigg & Grady 2010; Laird et al., 2011; Schilbach et al., 2008; Spreng & Grady 2010). Our results suggest that hypoconnectivity of the DMN could compromise these functions and result in delusional thinking. Hypoconnectivity within the DMN had been previously demonstrated in patients with AD (Agosta et al., 2012; Liu et al., 2014; Thomas et al., 2014; Chhatwal et al., 2013; Zhou et al., 2015; Greicius et al., 2004; Zhang et al., 2010). In AD, hypoconnectivity of the DMN often involves the precuneus (Greicius et al.; Agosta et al., Liu et al.), posterior cingulate (Greicius et al., 2004, Zhang et al., 2010), and hippocampus (Greicius et al.; Agosta et al., Liu et al.). But perhaps it is the specific decrease in connectivity of the IPL that contributes to delusions.

Functional alterations at rest involving IPL have been reported in patients with schizophrenia (Guo et al., 2014; Hinkley et al., 2011; Liu et al., 2016; Liu et al., 2017; Schilbach et al., 2016; Zhou et al., 2015b; Zhuo et al., 2017) and their first-degree relatives (Liao et al., 2012; Muller et al., 2013; Tang et al., 2015). Liu and colleagues found that drug-naïve schizophrenia patients showed significantly reduced coherence of the right IPL, as well as other regions including the bilateral precuneus, right middle frontal gyrus, and left superior temporal gyrus (Liu et al., 2017). Zhou and colleagues found that schizophrenia patients had decreased functional connectivity in the posterior parieto-occipito-temporal areas, including the IPL (Zhou et al., 2015b). Moreover, functional connectivity of IPL has specifically been linked to positive symptoms (Hinkley et al., 2011) and delusions (Guo et al., 2014) within schizophrenia. As well, individuals with parietal lobe epilepsy have been found to show psychosis (Ishii et al., 2006; Salanova et al., 1995). However, the parallel between delusions in AD and these other conditions is only speculative.

The IPL is a key region within the DMN involved in a wide range of cognitive functions (Arsalidou & Taylor 2011; Binder et al., 2009; Buckner et al., 2008; Bzdok et al., 2012; Caspers et al., 2006; Caspers et al., 2010; Daselaar et al., 2006; Glover 2004; Schilbach et al.,

2012; Seghier 2013; Spreng et al., 2009; Wagner et al., 2005). The IPL is responsible for semantic processing by integrating sensory information from different modalities, evaluating the information, and consequently planning a response (Binder et al., 2009; Torrey 2007; Zhang & Li 2014). Thus, impaired functioning of the IPL can overwhelm a person with sensory information and hinder their integration, and consequently impair the ability to make appropriate associations (Binder et al., 2009; Torrey 2007). The coactivation of IPL and precuneus and the PCC also plays a role in explicit memory, chiefly for the emotional connotation of explicit memory (Brand & Markowitsch 2008; Spreng et al., 2009; Wagner et al., 2005). The recall of explicit memories, especially autobiographical memory, comprises of recalling both facts and emotional cues. Therefore, impaired connectivity between these regions can alter the emotional connotation to a memory (Muller et al., 2013; O'Connor et al., 2010). Another major function of the IPL is to provide a stable egocentric reference frame for the representation of space (Land 2014; Lou et al., 2010; Seubert et al., 2008) and concept of self (Davey et al., 2016; Vogeley et al., 2001), including the ability for self-face recognition (Uddin et al., 2005; Yun et al., 2014). Related to the concept of self is inferring the mental state of others, a concept known as theory of mind, which has been shown to activate the IPL, anterior cingulate, and other areas in the frontal and temporal lobes (Brune & Brune-Cohrs 2006). Therefore, IPL dysfunction could decrease the capacity to accurately judge the mental state of others, which could falsely create the idea that others have harmful intentions, i.e. delusions of persecution. The IPL has a role in executive functions, a cognitive domain traditionally believed to be the sole responsibility of the frontal lobes. However, multiple tasks of executive function have been found to activate the IPL along with prefrontal areas (Buchsbaum et al., 2005; Wang et al., 2001). It has been posited that delusions represent “top-down” processes where individuals impose their own internal explanation in trying to interpret their experience, rather than bottom-up processing by logically using sensory information (Schilbach et al., 2008). Consistent with this notion, breakdown in regions involved in executive function may contribute to delusions.

The current study showed that the reduction in IPL connectivity in association with delusions was restricted to the left hemisphere. This is concordant with findings by Swanson et al. (2011), who showed markedly greater intrinsic fluctuation of the IPL on the left than right side in healthy controls, while patients with schizophrenia did not show lateralization in the IPL (Swanson et al., 2011). Therefore, asymmetric increased activity of the left IPL is associated with normality, and a disruption in the asymmetry is abnormal and is associated with pathological states such as schizophrenia (Frederikse et al., 2000). Consistent with this, the delusional group showed diminished left IPL connectivity. The type of delusion might also affect asymmetry of the IPL, with persecutory delusions being more left lateralized while misidentification delusions being more right lateralized (Holt et al., 2006). In our sample there were slightly more subjects with persecutory delusions (73%) than misidentification delusions (53%), which could have driven the left-sided association. IPL has also been found to show sexual dimorphism, with males having a larger left IPL than females (Frederikse et al., 1999). However, our delusional and non-delusional cohorts did not differ in the proportion of the sexes. The significance of the asymmetry is unclear, but the left IPL has been found to play a role in higher-order cognitive processes such as language (Cohen et al., 2000).

Contrary to part 1 of the current thesis, we did not find that vascular risk factors were associated with delusions. The sample size may have been too small to detect significant differences. Alternatively, since we relied on a clinical diagnosis of AD in part 3 as opposed to a neuropathological diagnosis in part 1, patients with significant vascular risk could have been diagnosed as vascular dementia and were consequently excluded from the study.

5.3.1 Limitations

Some limitations should be noted. Firstly, the sample size was relatively small, although it was sufficient to detect significant differences that are robust, withstanding conservative corrections. However, the small sample size may have restricted the power to detect further differences, such as in the frontal network. Secondly, the delusional cohort had significantly greater prevalence of hallucinations, depression, and irritability, which could have influenced the resting-state connectivity. A history of depression was higher in the delusional cohort, although it did not reach significance. In the future, comorbid neuropsychiatric symptoms, particularly depression, should be controlled. Thirdly, the extent to which these networks are disrupted may be dependent on the disease severity (Damoiseaux et al., 2012). Certain connections may be disrupted earlier in the disease course than other connections. Although the delusional and non-delusional groups were comparable in global cognition, they may both be at a stage where certain connectivity changes become more vulnerable. Another limitation is that connectivity may be affected by other factors, such as medication use. None of the delusional subjects were taking antipsychotic medication, and the proportion of subjects taking cognitive enhancers or anti-depressants were even in both groups, but the effects of other medication cannot be ruled out. Lastly, while fMRI is able to enlighten us on the functional connectivity between brain regions, the pathological process of neuronal damage remains to be clarified.

5.4 Summary of Chapter 5

Building on the findings from Chapter 4, Chapter 5 of the current thesis explored the resting-state functional connectivity associated with delusions. The DMN was a reliably activated component, and we found that patients with delusions showed decreased connectivity of the DMN. Decreased functional synchrony of the IPL with the rest of the DMN appears to be associated with delusions.

Chapter 6:

Conclusions and Future Directions

The current thesis aimed to investigate the neural correlates of delusions in AD. Understanding the complex pathophysiology of delusions requires a multimodal approach constituting of pathology as well as different neuroimaging modalities. Here, we examined the neuropathology (Chapter 3), the structural (Chapter 4) and functional resting-state (Chapter 5) brain architectures underlying delusions in AD.

6.1 Summary and Conclusion

The results of Chapter 3 demonstrated that psychotic symptoms are not associated with increased AD pathology (i.e. plaques and tangles), but are instead associated with Lewy body pathology as well as vascular pathology and vascular risk factors including hypertension and diabetes. The association between psychosis and AD pathology was restricted to the clinically diagnosed AD cohort and not in the neuropathologically confirmed cohort (Fischer et al., 2015). This suggests that the association between psychosis and increased AD pathology as previously reported in the literature is likely driven by clinical misdiagnosis of AD. The negative association is consistent with some previous research (Skogseth et al., 2008; Sweet et al., 2000). Combined, these findings suggest that Lewy bodies and cerebrovascular disease play important roles in the development of psychosis in AD. The link between vascular entities and psychosis has been previously hinted (Bassiony et al., 2000; Treiber et al., 2008), but no studies have investigated vascular effects using neuropathology. To our knowledge this is the first study to identify vascular pathology, specifically subcortical arteriosclerotic leukoencephalopathy, as being associated with psychosis. Chapter 3 also highlighted the importance of separating delusions and hallucinations rather than considering them as a

single “psychosis” entity. For instance, patients with delusions appeared to have a different clinical trajectory and have a weaker association with Lewy bodies than patients with hallucinations. Therefore, research should investigate the neural correlates pertaining to delusions separately from hallucinations.

The results of Chapter 4 showed that there are grey matter differences between delusional and non-delusional AD patients both after as well as prior to the clinical manifestation of delusions. Furthermore, there are differences in the longitudinal pattern of atrophy between the delusional and non-delusional cohorts. Patients who exhibited delusions had lower grey matter primarily in the prefrontal cortex compared to patients without delusions. The finding of frontal deficits is most consistently reported in the literature (Koppel et al., 2014c; Lee et al., 2007; Lee et al., 2009; Paulsen et al., 2000a; Paulsen et al., 2000b). The prefrontal cortex is responsible for producing rapid, unplanned reactions to internal and external stimuli. Therefore, a disruption in the ability to generate appropriate responses could contribute to delusional thoughts. Loss of prefrontal volume is also consistent with the theory of hypofrontality, which posits that frontal deficits that lead to poor insight may be an underlying cause of delusions (Aalten et al., 2005; Harwood et al., 2005; Paulsen et al., 2000a; Starkstein et al., 1996). Decreased insight, defined as the ability to be aware of the deficits and have intuitive understanding of the environment, can be what allows a patient with delusions to sustain his or her belief even in light of contradictory evidence. Predating delusional onset, the patients who develop delusions had higher grey matter in regions including the ventral medial prefrontal cortex, precuneus, IPL, and medial temporal cortex, as well as lower grey matter in the thalamus, superior frontal gyrus, and insula. Interestingly, the regions of higher grey matter, many of which are regions of the DMN, exhibited significant atrophy following the development of delusions. In contrast, the non-delusional cohort did not exhibit any significant clusters of atrophy over a similar follow-up period. This supports the notion that delusional patients undergo a more rapid disease progression. Specifically, increased atrophy of regions that are a part of the DMN may be central in the development of delusions, rather than isolated

atrophy in individual regions. This is the first longitudinal study to show that regions of grey matter atrophy following the expression of delusions overlap with the DMN.

Building on the findings from Chapter 4 implicating network disturbances, Chapter 5 investigated the resting-state connectivity of large-scale networks in association with delusions. Rs-fMRI is sensitive to functional brain organizational changes in asymptomatic adults that may otherwise not be detected using other modalities like in standard task-based fMRI (Sperling et al., 2009). Therefore it has valuable clinical utility as well as being an important tool that can provide greater insight into how brain information is integrated to give rise to human behaviours. We investigated two components that accounted for the greatest variability in brain oscillation—one that depicted the DMN as well as an anterior frontal network. The most important finding was reduced coupling of the IPL with the overall DMN in association with delusions. The DMN has been postulated to be related to self-monitoring, thinking about the self and others, autobiographical memory retrieval, envisioning the future, and mind wandering. Specifically within the DMN, the IPL has a crucial role in a wide range of cognitive functions, including semantic processing, multimodal sensory integration, providing emotional connotation to an explicit memory, inferring the mental state of others, concept of self, and executive functions (Torrey 2007). Therefore, breakdown of the DMN, specifically uncoupling of the IPL from the DMN, can compromise these important cognitive functions, which can contribute to misattribution and delusions.

Given the finding of an association between white matter pathology and vascular risk factors in association with psychosis, and that functional network connectivity may be impaired in those with delusions, it hints at a potential underlying mechanism for the development of delusions. Our results support that white matter pathology may damage the connecting fibres between nodes of the DMN, consequently impairing the cognitive abilities it subserves. Previous studies have found that increased WMH in fibre tracks

connecting parts of the DMN can cause microstructural damage and has the potential to disrupt functional connectivity (Papma et al., 2014; Taylor et al., 2016). To further test this hypothesis, we would use DTI to assess fibre tract connections in AD patients with delusions compared to those without delusions.

6.2 Significance

Given the debilitating outcomes associated with the delusional phenotype of AD and the lack of effective and safe treatments, a better understanding of delusions is critical for AD patients and their caregivers. Currently, the medications for psychosis in AD have been repurposed FDA and HPFB approved medication for schizophrenia, which might account for the high mortality and low efficacy in the AD population (Health Canada 2005; Herrmann & Lanctot 2006; Schneider et al., 2005). Elucidation of the underlying neurobiology and mechanisms of delusions is required to pave the way for novel treatments specific to AD. Appreciating the functional and structural brain changes associated with delusions could potentially lead to interventions, both pharmacologically and non-pharmacologically, to target these specific brain regions.

In the current study, we found biological differences between delusional and non-delusional AD patients, which could serve as biomarkers to progress novel treatments for these patients. We found that neurodegeneration does not occur in isolated locations, and the impact of degeneration in one area may affect the functions of other remote areas that are connected functionally. Recent studies have shown that changes in resting-state networks such as in the DMN predate anatomical changes. Therefore, the clinical implication is that biomarkers can be used to identify those who may be at risk of developing delusions, select patients who may benefit from treatment, and assess the efficacy of a treatment in clinical trials. For example, abnormal DMN pattern can be used to

identify those who may be at high risk of developing delusions so that they can be closely monitored (Fusar-Poli et al., 2012), and modifiable factors such as cardiovascular risk factors can be better controlled. By identifying those who may be at risk of developing delusions, early interventions that modulate networks such as repetitive transcranial magnetic stimulation (rTMS) and theta burst stimulation (TBS) could be used. These alternative therapeutic approaches have already been shown to successfully promote neuroplasticity (Dayan et al., 2013; Freitas et al., 2009; Halko et al., 2010; Huang et al., 2005; Uddin et al., 2006; Wang et al., 2014). Furthermore, the IPL has been proposed as a prominent site for the use of TMS in patients with schizophrenia (Freitas et al., 2009; Uddin et al., 2006). As such, the utility of these novel techniques to increase DMN connectivity in delusional AD patients remains a future goal. However, the use of resting-state imaging as a biomarker at an individual level remains to be established. A better understanding of the pathophysiology of delusions in AD can also help to advance more accurate mouse models to study psychosis. Currently, the candidate mouse model for psychosis in AD, rTg(tauP301L)4510, is a transgenic tau mouse with heavy frontal tau burden (Koppel et al., 2014b). However, if psychosis in AD is not associated with increased tau, or involves other brain region abnormalities, then the mouse model for psychosis would need to be revised.

6.3 Future Directions

The current thesis began to explore the neuropathology and imaging correlates of delusions in AD, but there remains a lot to learn. There are several important questions that remain to be addressed in future studies.

1. Investigate how DMN connectivity evolves longitudinally

There may be different network changes at different stages of the disease, so it is important for future studies to investigate RSN connectivity at multiple time points to elucidate the

changes throughout as well as before the disease. In Chapter 4, we found that there are gray matter anatomical differences between delusional and non-delusional patients even before the manifestation of delusions. Therefore it is likely that resting-state abnormalities exist prior to the development of delusions as well. Damoiseaux et al. speculated that hyperconnectivity might precede hypoconnectivity as a sign of brain remodelling (Damoiseaux et al., 2008). Therefore, it is crucial to learn the longitudinal network pattern. If there is a specific network pattern that can be identified prior to the onset of delusional symptoms, it can be used as a surrogate marker of preclinical delusions.

2. Compare resting-state functional connectivity in other patient populations with psychosis

Unifying the results from other psychotic disorders could lead to a more nuanced model of psychosis, as there may be a common pathophysiology underlying psychosis. The results of our study showed many parallels to patients with schizophrenia, but a direct comparison utilizing the same imaging parameters and analysis technique should be a future step.

3. Other factors that can affect network connectivity

Future studies should investigate the potential effects of other factors that can contribute to network disconnectivity, such as medication (e.g. antipsychotic or cholinesterase inhibitors), environmental factors (e.g. diet and exercise), gender, genetics (e.g. *APOE* genotype), and biochemical factors (neurochemical imbalance). For example, comparing medication naïve with medicated delusional AD patients can shed light on how medication can impact resting-state connectivity. There have already been some studies showing that the *APOE* $\epsilon 4$ allele is related to DMN attenuation (Machulda et al., 2011; Westlye et al., 2011; Yuan et al., 2016), but the interaction between *APOE* $\epsilon 4$ and delusions on DMN connectivity remains unknown. Future studies should replicate Chapter 5 of the current thesis, but include *APOE* $\epsilon 4$ status as an independent variable in a multivariate analysis.

4. Understanding the relationship between network connectivity and clinical correlates

In Chapter 5, we found that delusions were associated with functional changes in the DMN. However, the relationship between the network changes and clinical correlates are unclear. One of the limitations of rs-fMRI is that the unconstrained task may prompt over-interpretation of results that cannot be fully validated without cognitive or behavioural data. Future studies should correlate behavioural and cognitive data to network connectivity, or use task-based fMRI to elucidate the function of the activated regions. It is also unclear if there is a threshold of disruption to DMN that is necessary to generate delusions (e.g. uncoupling of 1-2 hubs), or if decreased integration of IPL is sufficient. Future studies can use animal models to modulate different components of the DMN, as well as the extent of disconnection, to elucidate if disruption to certain hubs is more amenable to cause delusions, and if a certain level of disconnect is required. Using an experimental design rather than a correlational design may determine the causal relationship between RSN abnormalities and delusions.

5. Using other imaging modalities

Other imaging modalities should be employed to obtain a more complete picture of the brain changes associated with delusions. As we found that vascular pathology and vascular risk factors may contribute to delusions, it is important to explore using DTI how delusions are related to white matter structural tracts. We hypothesize that vascular lesions impair white matter tracts, which in turn disrupt network connectivity.

6. Consider how psychosis severity affects outcome measures

In the current study, subjects were dichotomized into delusional or non-delusional based on the NPI. Unfortunately we could not separate the analysis by severity due to the small sample size. It would be of importance in future studies to investigate if delusional severity is ordinally associated with outcome measures.

6.4 Conclusion

In conclusion, the results of the current thesis suggest that delusions in AD are associated with decreased functional synchronicity within the DMN through atrophy of key nodes within this network. Decreased integration of the IPL within DMN may be a key contributor to delusions. It is possible that arteriosclerotic leukoencephalopathy and vascular risk factors induces psychosis by impairing DMN connectivity (Son et al., 2015), but further evidence is needed to verify this association.

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