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Identifying neuroimaging and genetic correlates of delusions and hallucinations in Alzheimer's disease

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Abstract

The co-occurrence of psychotic symptoms and Alzheimer's disease (AD) is a devastating phenotype that affects around 50% of individuals with AD. We hypothesized that distinct interactions between brain structures and genetic variants in dopaminergic, cholinergic and glutamatergic neurotransmitter systems may be associated with the presence of hallucinations and delusions in AD. Using the Alzheimer's Disease Neuroimaging Initiative, we identified participants that presented with symptoms of delusions, hallucinations, or both symptoms. PLS-CA was used to identify differences in patterns of interactions between 15 single nucleotide polymorphisms and 82 neuroanatomical regions of interest between AD patients endorsing symptoms of delusions, hallucinations, and matched AD controls. Binary logistic regression analysis was used to cross-validate identified neuroanatomical differences. Results provide preliminary evidence that genetic variants in the glutamatergic system, along with regional brain changes, may uniquely identify those with hallucinations. A trend towards significance was also found which suggests that atrophy to the frontal lobe coupled with preservation of temporal lobe structures may be associated with symptoms of delusions in patients with AD. Overall, results provide evidence of a unique signature of neuroimaging and genetic interactions which may be associated with the presence of different psychotic symptoms in AD.

Keywords

Alzheimer's disease, hallucinations, delusions, psychosis, single nucleotide polymorphisms, cholinergic system, dopaminergic system, glutamatergic system, neurotransmitters, Magnetic Resonance Imaging, Partial Least Squares Correspondence Analysis.

Co-Authorship Statement

All data for this study was obtained from the Alzheimer's Disease Neuroimaging Initiative. I completed all aspects of data cleaning, extraction, analysis, and thesis writing with feedback from Dr. Elizabeth Finger. I received assistance with data analysis and preprocessing from Derek Beaton and Andrew Robertson. All R scripts used for the PLS-CA were created by Derek Beaton and Andrew Robertson. GWAS data was preprocessed and imputed by the lab of Dr. Jo Knight, in particular by Sejal Patel at the University of Toronto.

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List of Abbreviations

AD	Alzheimer's disease
SCD	Subjective cognitive decline
MCI	Mild cognitive impairment
MoCA	Montreal cognitive assessment
aMCI	Amnestic mild cognitive impairment
naMCI	Non-amnestic mild cognitive impairment
EOAD	Early-onset Alzheimer's disease
LOAD	Late-onset Alzheimer's disease
APOE	Apolipoprotein E
NFTs	Neurofibrillary tangles
NPS	Neuropsychiatric symptoms
BPSD	Behavioural and psychological symptoms of dementia
NPI	Neuropsychiatric inventory
NPI-Q	Neuropsychiatric inventory questionnaire
AD+P	Alzheimer's disease with psychotic symptoms
SPECT	Single photon emission computed tomography
PET	Positron emission tomography
AD+D	AD with delusions
LBD	Lewy body dementia
AD+H	AD with hallucinations
ACh	Acetylcholine

GWAS	Genome-wide analysis studies
SNP	Single nucleotide polymorphisms
COMT	Catechol-O- methyltransferase
ADNI	Alzheimer's Disease Neuroimaging Initiative
MRI	Magnetic Resonance Imaging
CDR	Clinical dementia rating scale
MMSE	Mini-mental state exam
TIV	Total intracranial volume
QC	Quality control
IBD	Identity by descent
MAF	Minor allele frequency
CEU	Utah residents with ancestry from northern and western Europe
YRI	Yoruba in Ibadan, Nigeria
JPT	Japanese in Tokyo, Japan
TSI	Tuscans in Italy
CHB	Han Chinese in Beijing, China
MDS	Multidimensional scaling
BCHE	Butyrylcholinesterase
CHRNA7	Cholinergic Receptor, Nicotinic Alpha 7 Subunit
DRD1	Dopamine Receptor D1
DRD2	Dopamine Receptor D2
DRD3	Dopamine Receptor D3
NMDA	N-methyl-D-aspartate
GRIN2A	Glutamate Ionotropic Receptor NMDA Type Subunit 2A

GRIN2B	Glutamate Ionotropic Receptor NMDA Type Subunit 2B
GRIN3A	Glutamate Ionotropic Receptor NMDA Type Subunit 3A
GRIN3B	Glutamate Ionotropic Receptor NMDA Type Subunit 3B
PLS-CA	Partial least squares correspondence analysis
ROI	Region of interest
AD-DH	AD without symptoms of delusions or hallucinations
AD	AD with both symptoms of delusions and hallucinations
PCA	Principal component analysis
FDG-PET	Fluorodeoxyglucose positron emission tomography

Chapter 1

1 Literature Review

1.1 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the most common cause of dementia. It affects close to 560,000 individuals in Canada alone and around 44 million people worldwide with the prevalence projected to double in the next ten years [1,2]. Importantly, the cognitive and functional deficits that arise from AD are more advanced than typical age-related cognitive decline and may present many years prior to an established clinical diagnosis of AD. With a growing aging population in Canada and worldwide, AD is not only a pressing concern for individuals and care-givers, but also represents a much larger public health issue. As such, research endeavors aiming to identify and characterize the underlying biological substrates contributing to the progression of AD and its associated symptoms are increasingly important as a starting avenue for the development of therapeutic interventions.

1.1.1 Stages of Cognitive Impairment and Progression to Alzheimer's Disease

AD is associated with gradual cognitive decline, with the specific disease trajectory for each individual being modulated by a combination of biological, social and psychological factors. Initial indications of prodromal AD are often reported as subjective cognitive decline (SCD) with patients endorsing symptoms of worsening cognitive function without clear impairments on cognitive screening tests [3,4]. As cognitive functions decline, patients may progress to develop Mild Cognitive Impairment (MCI) – characterized by a mild-moderate degree of cognitive impairment with preserved activities of daily living. A diagnosis of MCI is established through a comprehensive patient history and validated cut-off scores on neuropsychological testing including the Mini Mental State Exam (MMSE) [5] and the Montreal Cognitive Assessment (MoCA)[6,7]. An important distinction to note, is that those with MCI can be categorized into two major subgroups – amnestic MCI (aMCI) and non-amnestic MCI (naMCI), with the key distinguishing feature between the latter and the former being the predominance of memory impairments [8]. aMCI is often referred to as MCI due to AD, given its increased risk of progression to AD, with one study identifying an 8.5-fold increased risk for those with probable aMCI of converting to dementia [9]. This distinction has been further supported by structural

neuroimaging studies which implicate a greater reduction in volume and cortical thickness of key memory structures such as the hippocampus and the entorhinal cortex in patients with aMCI when compared to naMCI and healthy older controls [10]. Eventual progression to AD is characterized by severe cognitive and functional impairments that limit one's ability to carry out activities of daily living. These symptoms include memory loss, impaired reasoning and judgement, and changes in personality and behaviour – likely attributable to advanced neurodegeneration that hinders the brain's ability to compensate for disruptions in regional cortical networks.

Early-Onset Alzheimer's Disease (EOAD). About 5.5% of individuals diagnosed with AD are affected by early-onset or familial AD [11]. EOAD differs from late-onset Alzheimer's disease (LOAD) in that it affects individuals who are less than 65 years of age. Individuals with EOAD with a family history of AD may present with genetic mutations linked to three key genes – the Amyloid Precursor Protein [12], Presenilin 1[13], and Presenilin 2 [14]. Mutations in these genes have been found to be associated with the accumulation of beta-amyloid in the brain contributing to increased plaque pathology.

Late-Onset Alzheimer's Disease (LOAD). LOAD is a term used to classify individuals who develop AD after the age of 65. The greatest risk factor for LOAD is age, with the risk of AD doubling every 5 years after the age of 60 [15]. In addition to age, other genetic and environmental factors may also contribute to the development of LOAD. The major genetic risk factor for LOAD is the apolipoprotein E (APOE) gene, a key gene in the central and peripheral nervous system involved in lipid transport [16,17]. In particular, when compared to the more common E3/E3 genotype, those with one copy of the E4 allele have a three-fold increased risk of AD, while those with two copies of the allele have an 8-12 fold increased risk [18,19]. The mechanism by which the E4 allele is thought to contribute to AD pathology is through the decreased ability to clear beta-amyloid, leading to the aggregation of beta-amyloid into fibrils and plaques which subsequently contribute to disruptions in synaptic connectivity and neurodegeneration in AD [20].The immunoreactivity of ApoE has also been shown to be associated with amyloid deposits and neurofibrillary tangles [21]. Protective factors against AD include carrying the E2 allele of the APOE gene, more years of formal education, physical activity, and social

engagement [22–25]. Both increased educational attainment and social activity are thought to be protective against AD due to their proposed ability to increase cognitive reserve. In this case, cognitive reserve refers to the brain's ability to adapt to pathological changes arising from AD, by using either compensatory strategies or other means of cognitive appraisals. Overall, these observations suggest that increased cognitive reserve may make individuals more resilient to early disruptions in normal cognitive functioning arising from the pathology of AD, and delay the onset of identifiable cognitive impairment [26–28].

1.1.2 Neuropathology of Alzheimer's disease.

The two cardinal pathological features of Alzheimer's disease – beta-amyloid plaques and neurofibrillary tau tangles (NFTs), were first identified and described by Alois Alzheimer[29,30]. The aggregation of extracellular beta-amyloid, in particular the neurotoxic Aß42 form of the protein, has been identified to lead to the formation of oligomers and senile plaques throughout the brain in patients with AD [31,32]. Beta-amyloid has also been implicated in the amyloid cascade hypothesis which postulates that AD progression is driven by the accumulation of insoluble extracellular beta-amyloid plaques. This accumulation is thought to disrupt downstream processes and contribute to the abnormal phosphorylation of tau proteins. Collectively, both the beta-amyloid and tau pathology arising from this cascade is thought to lead to disruptions in synaptic connectivity and ultimately neuronal death [33].

NFTs are abnormally phosphorylated tau proteins localized within neurons. The accumulation of phosphorylated tau proteins leads to misfolding and disruption of intraneuronal cytoskeletal architecture resulting in decreased cell stability [34–36]. NFTs are initially found regionally distributed in cortical and subcortical structures involved in memory and cognitive function, with their presence in these regions corresponding with early symptoms characteristic of AD. These include structures within the temporal lobe such as the entorhinal cortex, hippocampus, amygdala and posterior parahippocampal regions [37]. Overtime, paralleling disease progression, NFTs become more dispersed and affect structures involved in language, personality and motor coordination. Given the positive correlation between NFT pathology and AD progression, clinical evaluations characterize AD progression using NFT pathology as a severity and stage marker of AD

[38]. Taken together, both beta-amyloid plaques and NFTs are associated with disruptions in normal cell-signaling which ultimately manifests biologically as localized cortical atrophy in regions affected by these lesions, and behaviorally as impairments in memory, language and other cognitive and non-cognitive domains.

1.1.3 Neuropsychiatric and behavioural symptoms in Alzheimer's disease

In addition to cognitive impairments, many patients with AD also develop non-cognitive symptoms such as neuropsychiatric symptoms which are interchangeably referred to as behavioural and psychological symptoms of dementia. The prevalence of these symptoms in patients with dementia has been shown to be nearly universal with close to 97% of patients developing at least one neuropsychiatric symptom [39]. The comorbid presentation of AD with neuropsychiatric symptoms has been shown to be associated with more rapid cognitive decline, higher rates of institutionalization, and greater care-giver and financial burden [40–42]. In a clinical setting, the most widely used assessment for neuropsychiatric symptoms in individuals with dementia is the Neuropsychiatric Inventory (NPI)[43]. The NPI evaluates the frequency and severity of 12 neuropsychiatric symptoms including delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetitive and eating abnormalities. The NPI has also been adapted into a validated brief clinical form known as the Neuropsychiatric Inventory Questionnaire (NPI-Q)[44] which assesses the presence or absence of these neuropsychiatric symptoms. A systematic review by Zhao and colleagues (2016) found that in patients with AD, apathy was the most common NPS with a prevalence of 49%, while euphoria was the least common with a prevalence of 7%. Further studies have used techniques such as factor analysis to categorize these symptoms into distinct subgroups including, 1) Hyperactivity (agitation, disinhibition, irritability, and aberrant motor behaviours); 2) Psychosis (hallucinations, delusions, night-time behaviour disturbance); 3) Affective (depression, anxiety); and 4) Apathy [45]. Of particular importance is that the psychosis subsyndrome was associated with the highest overall NPI score, suggesting that the presence of these symptoms may further exacerbate cognitive and functional decline in patients with AD.

1.1.4 Primary Psychosis vs. Secondary Psychosis

Psychotic symptoms are common and characteristic phenomenon of primary psychotic disorders such as schizophrenia but may also arise as presenting symptoms in other diseases [46]. When psychosis arises as a symptom of a pre-existing medical condition, for example as a symptom of delirium [47], neurologic, or neurodegenerative disorder, this presentation is referred to as secondary psychosis. A key distinguishing feature of primary psychosis from secondary psychosis arising from AD, is that on cognitive screening, those with primary psychosis retain the ability to remain oriented to the world around them [48]. When comparing the two most common psychotic symptoms – delusions and hallucinations, in those with schizophrenia and AD, a few key differences are important to note. Firstly, delusional symptoms in schizophrenia tend to be more complex and bizarre, while in AD delusions tend to be simpler, with the most common being paranoid delusions such as delusions of theft or infidelity [49,50]. This distinction is supported by neuroimaging studies which further suggest that delusions in AD may arise as a result of progressive memory and cognitive impairments [51,52], which in turn may generate states of confusion or paranoia ultimately leading to delusional symptoms [53]. Secondly, individuals with schizophrenia also predominantly experience auditory hallucinations but may also experience hallucinations in other sensory modalities. The hallucinations experienced by those with schizophrenia are typically described as Schneider's first-rank symptoms indicating a loss of self vs. non-self distinction (e.g. hearing third-person voices talking to one another about oneself, intrusive second-person voices commenting on an individual's thoughts and behaviours)[54]. In contrast, visual hallucinations tend to be more common in individuals with AD and include seeing people or animals [55]. While the presentation of psychotic symptoms may vary in those with schizophrenia and AD, neuroimaging studies have implicated similar brain regions suggesting an overlapping neuropathology, discussed in further detail below, which may contribute to the development of hallucinations and delusions in these disorders.

1.2 Psychosis and Alzheimer's disease

The co-occurrence of psychotic symptoms and AD is a devastating phenotype (AD+P) that affects close to 40% of individuals with AD [41], making it one of the most common

psychotic disorders – second only to schizophrenia [49,56]. When describing psychotic symptoms in AD, the two most common symptoms that fall under this category are delusions and hallucinations. Delusions are defined as persistent false beliefs that are resistant to reasoning and are independent of any cultural beliefs. Hallucinations are defined as sensory perceptions, of any sensory modality, that occur in the absence of any external stimuli. Notably, in AD, the presence of these symptoms begins early in the disease course and remains persistent over time. For example, a study by Paulsen and colleagues (2000)[57], showed that in a sample of 329 AD patients, 20% had symptoms of hallucinations or delusions at baseline, with the cumulative incidence increasing to around 51% at four years follow-up. When compared to other neuropsychiatric symptoms in AD, such as agitation, aggression or disinhibition, the grouping of hallucinations and delusions into one overarching category in many factor analytic and latent class analysis studies, suggests that these symptoms may have some shared neural correlates [45,58,59]. But when broken down further, more recent studies suggest a divergence in psychotic symptomatology and consequently raise the question of whether the final pathway that leads to the presentation of hallucinations and delusions in AD may differ [60,61]. Studies that have subdivided psychotic symptoms to identify the individual prevalence of delusions and hallucinations have consistently found that delusions tend to be more common in those with AD when compared to hallucinations [62,63]. In a systematic review, the prevalence of delusions was found to range from 9 – 59% in individuals with AD, with a pooled-prevalence of approximately 31%, while the prevalence of hallucinations was found to range from 6 – 41%, with a pooled prevalence of approximately 16% [64]. Given that delusions and hallucinations may be associated with distinct biological correlates, developing a better understanding of how they uniquely arise may provide greater insight into more specific and targeted treatment options for each symptom.

1.2.1 Delusions in Alzheimer's disease: Cognitive models and neuroanatomical correlates

Investigations into the neuroanatomical and pathological correlates of delusions in AD have led to the proposition of three key theories that may explain the etiology of delusions in AD [65]. The first model is known as the hypofrontality model which postulates that delusions in AD arise as a result of disrupted frontal lobe function either

due to atrophy to frontal brain regions or hypoperfusion in these areas. Evidence in support of this model include neuroimaging studies using single photon emission computed tomography (SPECT) and positron emission tomography (PET) which suggest that individuals with AD and delusions (AD+D), when compared to controls, have hypoperfusion in frontal brain regions [66–68]. A limitation of this theory is that it presupposes that all delusional symptoms may arise as a result of frontal pathology without acknowledging that different types of delusions for example, misidentification and paranoid delusions may have additional unique neural substrates. For example, an earlier PET study of AD patients with misidentification delusions, found that patients with these delusions compared to AD controls, had more pronounced bilateral cingulate and basal ganglia hypometabolism, in particular in regions of the orbitofrontal, middle temporal, anterior and posterior cingulate, left caudate nucleus, left lentiform nucleus, and the left calcarine[69]. Results of this study suggest that it may not just be the frontal lobes that are implicated in AD+D, but rather coordinated networks of regions which may contribute to the presence of specific types of delusions in AD. In particular, given the involvement of the basal ganglia, there may be limbic loops extending from subcortical structures to frontal regions of the cortex which may explain the distressing emotional aspects of delusional symptoms.

The second theory proposes that delusions may be non-cognitive manifestations of AD and are based on research findings that suggest that individuals with AD+D may have greater behavioural impairments independent of AD neuropathology when compared to those without delusions [70,71]. More specifically, this theory proposes that individuals with AD+D do not significantly differ in cognitive abilities on neuropsychological testing when compared to individuals without delusions, but that they do have more severe behavioural symptoms such as aggression and other activity disturbances. As such, according to this theory, scores on neuropsychological testing alone would not be predictive of the subsequent development of delusions in AD. From a neuropathological level, Sweet and colleagues (2000)[71] found that AD+P was not associated with increased severity of plaque and tangle formation when the sample was controlled for the presence of Lewy bodies. A few limitations of this theory include the lack of consideration that perhaps aggressive behaviours may make individuals more prone to psychosis or vice

versa. Namely, those with symptoms of aggression may be more inclined to exhibit paranoid delusions in which they believe that others are stealing from them or fear persecution from those around them. Contrarily, delusional belief that others are out to get them, may actually perpetuate aggressive behaviours. As such, it would be important to dissociate whether delusions exhibited by those with other behavioural symptoms are in fact organic delusions or whether they occur in response to, or a result of, aggressive behaviours and can be resolved upon treatment of aggressive symptoms.

In contrast, the third theory proposes that AD+D may arise as a result of the pathophysiology of AD. With respect to this theory, the pathophysiology of AD is defined in reference to the characteristic features of AD – namely amyloid plaques and neurofibrillary tangles. Unlike the aforementioned theory, this model proposes that the increased severity of these plaques and tangles may contribute to the presence of delusions in AD. In support of this model, studies have found independent associations of psychotic symptoms with neurofibrillary tangle density [72] and senile plaques [73]. These differences in findings when compared to the previously described theory could be attributed to the lack of control for those with Lewy body dementia (LBD), as well as different methodological approaches with regards to specific brain regions that were investigated.

While these theories have been used to describe the biological correlates of delusions more generally, it is important to note that delusions in AD can be categorized into two major subgroups – paranoid and misidentification delusions [74]. Paranoid delusions include delusions of persecution, theft, as well as infidelity. Misidentification delusions include Capgras syndrome in which an individual believes someone close to them has been replaced by an imposter; TV sign, in which they believe that characters or situations depicted on TV shows are real; and phantom boarder syndrome in which they believe that a stranger is inhabiting their house. In contrast to the theories proposed above, a review of more recent studies suggest that paranoid and misidentification delusions may have distinct neuropathological correlates, with paranoid delusions being associated with more frontal impairments and misidentification delusions with medial temporal lobe structures [75].

In addition to these three theories, many studies also suggest a hemispheric lateralization for delusions, with the majority of studies implicating right hemisphere dysfunction [57,67,76]. In particular, it has been hypothesized that atrophy in the right hemisphere may lead to changes in memory, thinking, reality monitoring failure, and impairments in autobiographical memory retrieval, which in turn may manifest as delusional judgements or beliefs that can be communicated if there is relative preservation of the left hemisphere [77,78]. Collectively, these theories suggest that there may be multiple factors contributing to the pathology of AD+D, with the majority suggesting involvement of the frontal lobes as being the driving factor behind delusional beliefs.

1.2.2 Hallucinations in Alzheimer's disease: Cognitive models and neuroanatomical correlates

Hallucinations in Alzheimer's disease (AD+H) can be associated with any sensory modality but the two most common types of hallucinations in AD tend to be visual and auditory [79–81]. Understanding the underlying biological correlates of hallucinatory symptoms is increasingly important since previous research suggests that the presence of hallucinations in AD is associated with more rapid cognitive deterioration and an increased risk of mortality [82–84]. With regards to the neuroanatomical correlates of hallucinations, some studies suggest the involvement of corresponding sensory brain regions with particular modalities of hallucinations (i.e. primary auditory cortex in auditory hallucinations, visual cortex for visual hallucinations) and go further to suggest that specific brain regions may be linked to the content of hallucinations [85]. Being able to correlate hallucinations with specific brain regions is particularly important because it may suggest that localized pathological abnormalities are associated with subtypes of hallucinations and therefore help to guide more targeted treatment options.

When looking at the neuroanatomical correlates of hallucinations in AD specifically, there have been conflicting hypotheses as to what may generate these symptoms. Some studies suggest that visual hallucinations may arise as a result of occipital lobe atrophy [86], while others suggest that relative preservation of the cortex is necessary to generate psychotic symptoms in AD [87]. In support of the posterior atrophy and hypometabolism model, one study found that subcortical white matter lesions in occipital regions –

hypothesized to be an indication of abnormalities in the primary visual pathway, were associated with AD+H in the absence of any visual acuity deficits [88]. Controlling for visual acuity is particularly important in an elderly population, given that other neurologic deficits, such as Charles Bonnet syndrome may also give rise to hallucinations [89]. Charles Bonnet syndrome is also characterized by symptoms of visual hallucinations but in this case these symptoms arise as a result of vision loss from eye conditions such as macular degeneration. In addition to the neuroanatomical correlates of hallucinations, one study also suggests that hallucinations in AD are associated with a decline in inhibitory control and difficulty in suppressing intrusive memories or thoughts which may then be misattributed to external stimuli [90]. Overall, given the heterogeneity of hallucinations, there is no clear consensus in the field as to what may be the underlying mechanism of hallucinations in AD, but the existing literature does suggest that brain regions involved in different sensory process may be associated with hallucinations of the same modality.

1.3 Genetic Correlates of Psychosis

While there is significant evidence that regional brain atrophy may contribute to the formation of hallucinations and delusions, what remains unclear is why a proportion of individuals with AD develop psychotic symptoms while others remain asymptomatic throughout their disease course. To address this variability, some studies have looked into the heritability of AD+P and have found evidence of a familial aggregation of AD+P [60,91,92]. These studies have also identified a heritable component, with one study estimating the heritability of LOAD and psychotic symptoms to be around 61% [93]. Collectively, these studies provide strong evidence in support of a genetic component to AD+P and highlight the importance of understanding the genetic factors which may contribute to the development of psychotic symptoms in AD. Genetic variants in neurotransmitter pathways are of particular interest, given the modulation of psychotic symptoms by treatments that target neurotransmitters in several neuropsychiatric disorders. More specifically, studies that have examined neurotransmitters involved in the development of schizophrenia as well as other neurodegenerative diseases that present with psychiatric symptoms, such as AD, have implicated a role of the cholinergic,

dopaminergic and glutamatergic neurotransmitter system in the development of delusions and hallucinations.

1.3.1 Cholinergic System

One of the pathologies of Alzheimer's disease is the loss of neurons in the Nucleus Basalis of Meynert, a major source of cholinergic innervation to the cerebral cortex[94,95].The neurotransmitter acetylcholine (ACh) plays an important role in memory, arousal and learning. Consequently, the cholinergic deficiencies which arise in AD have led to the development of the cholinergic hypothesis in explaining the cognitive and behavioural changes, including neuropsychiatric symptoms, in AD [96,97]. The cholinergic hypothesis of neuropsychiatric symptoms in AD proposes that the projections from the nucleus basalis, which enables limbic-neocortical interactions, becomes disrupted and consequently alters emotional and motivational states, leading to the observed behavioural changes in AD [98]. Recent genome-wide analysis studies (GWAS) have begun to investigate single nucleotide polymorphisms (SNPs) in neurotransmitter systems to identify if certain polymorphisms may be risk factors for the development of psychosis in AD [99]. For example, a significant association between the development of delusions and a polymorphism (rs6494223) in the alpha-7 nicotinic acetylcholine receptor gene has been identified [100]. Moreover, patients treated with donepezil, a cholinesterase inhibitor, have shown improvements in delusional symptoms suggesting that imbalances in the cholinergic system, in particular within frontal brain regions, may be associated with the emergence of delusional symptoms in AD[101].

1.3.2 Dopaminergic System

The dopamine system has been extensively studied in relation to the positive and negative symptoms of schizophrenia. More specially, the dopaminergic hypothesis postulates that the positive symptoms of schizophrenia (i.e. hallucinations, delusions etc.) may arise as a result of increased dopamine levels in the striatum, stemming from increased D2/D3 receptor density [102,103]. Given the findings that symptoms of psychosis may arise as a result of dopamine irregularities, studies have likewise examined the effect of dopamine specific polymorphisms and the development of psychotic symptoms in

neurodegenerative diseases. One such study by Sweet and colleagues (1998)[104], found that polymorphisms in the dopamine D1 and D3 receptor conferred a moderate risk of developing psychotic symptoms in AD. Similarly, a polymorphism in the catechol-O-methyltransferase (COMT) gene, which leads to the upregulation of striatal dopamine, has been shown to be a risk factor for the development of psychosis in AD [105].

1.3.3 Glutamatergic System

The glutamate system is likewise an appropriate candidate system to assess in relation with psychotic symptoms given that abnormal glutamate activity in schizophrenia is hypothesized to contribute to the development of hallucinations and delusions. Studies such as those conducted by Mogahaddam et al., (1997)[106] and Bickel and Javitt (2009)[107], provide support that antagonism of NMDA receptors elevates extracellular glutamate levels which may in turn lead to the development of psychotic symptoms similar to those seen in schizophrenia. On the other hand, excessive NMDA activity is associated with neurotoxicity which can lead to neuronal cell death, as can been seen in many neurodegenerative diseases such as AD [108]. To further support the role of the glutamate system in the development of psychotic symptoms, Begni and colleagues (2003)[109], found that the G1001C polymorphism in the Glutamate Ionotropic Receptor NMDA Type Subunit 1, in particular the C allele, was significantly associated with an increased risk of Schizophrenia (OR = 2.04). Through examining the functional effects of the G1001C polymorphism, the authors identified that this polymorphism may exert its biological effects by altering the consensus sequence in the nuclear factor kappa-light-chain enhancer of activated B-cells (NF-kB) transcription factor, a protein complex involved in DNA transcription. As such, investigating polymorphisms in the glutamate system may provide additional information on how psychotic symptoms may arise in AD.

1.3.4 Current Treatment Approaches

Current treatment approaches for psychotic symptoms in AD include the use of atypical antipsychotics such as risperidone, olanzapine, and aripiprazole but have been associated with limited efficacy and severe side effects in patients with dementia, deriving from a lack of biological specificity. A review of 16 placebo-controlled trials suggests that the

use of risperidone may modestly improve psychotic symptoms in AD but is also associated with severe adverse outcomes including cerebrovascular and extrapyramidal side effects. Given the modest efficacy and vast side-effect profile, it was concluded that risperidone should not be used to routinely treat patients with AD+P [110]. A subsequent review identified that those with more severe symptoms of AD+P were those that may benefit the most from risperidone treatment [111]. Aside from risperidone, a clinical trial of aripiprazole in patients with a definitive diagnosis of AD+P, showed only a modest benefit when compared to placebo in improving psychotic symptoms. One identified benefit of aripiprazole when compared to other atypical antipsychotics, was that it was associated with minimal adverse side effects in patients with AD, although it did have minor negative effects on cognition [112]. However, it is also important to note that a review looking at the mortality rates associated with general atypical antipsychotic use found that there was an increased risk of mortality in patients with dementia that used these drugs (OR: 1.54)[113]. These findings of adverse and limited side-effects associated with current treatments for psychosis in AD, reiterate the importance of identifying more specific treatment options that target psychotic symptoms in AD. This is particularly important given that earlier interventions may improve the quality of life of those with AD+P, reduce long-term health care costs, and reduce the risk of institutionalization.

1.4 Neuroimaging and Genomics

Previous research has examined whether regional brain changes or genetic polymorphisms in neurotransmitter systems may give rise to psychotic symptoms. However, the results to date have been inconsistent because of a lack of dissociation of psychosis into the different subtypes. In addition, few studies have linked brain imaging and genetics together to investigate how the interaction between these two factors may mediate the presence of hallucinations and delusions in AD specifically. A previous study using neuroimaging genomics (the integration of neuroimaging and genetic techniques) and machine learning to predict AD, showed that adding genetics (in particular SNPs) to other imaging modalities may help improve the classification accuracy of AD [114]. One other study used large scale brain mapping for gene discovery to look specifically for SNPs that may be associated with temporal lobe volume. This study found that the risk

allele for rs10845840 located in the GRIN2B gene was associated with lower temporal lobe volume and overrepresented in AD/MCI subjects when compared to controls [115]. Although these studies did not look at particular symptoms of AD, these findings suggest that considering the interaction between neuroimaging and genetic factors may provide additional valuable information to aid in classification of participants. This is particularly important for psychotic symptoms in AD, given that hallucinations and delusions may arise as a result of imbalances in different neurotransmitter systems which may become more pronounced as a result of regional brain changes arising from AD.

1.5 Rationale and Hypothesis

The purpose of this study was to investigate the relationship between regional brain changes and genetic polymorphisms in neurotransmitter systems and the presence of hallucinations and delusions in AD. Given prior findings that there may be anatomical variations in individuals with AD, we sought to investigate whether these differences may indicate different phenotypes of AD. In particular, with regards to psychotic symptoms in AD, studies suggest that the frequency of these symptoms may vary across individuals with AD, with some individuals developing psychosis and others remaining asymptomatic throughout their disease course. Furthermore, there remains limited evidence and consensus in the literature with regards to particular brain regions that may be associated with symptoms of hallucinations and delusions. As such, we hypothesized that the *interactions* between regional brain structures and genetic variants in cholinergic, dopaminergic or glutamatergic neurotransmitter systems would be associated with symptoms of psychosis in AD, and that the distinct nature of these interactions would differ for those with delusions when compared to those with hallucinations. More specifically, we rationalized that investigating the interactions between regional brain changes and genetic variants would be critical in identifying whether the functional effects of specific genetic polymorphisms are unmasked as a result of regional brain changes arising from AD. We predicted that delusions and hallucinations are predominantly caused by the interaction of right frontal brain changes and genetic polymorphisms in dopaminergic, cholinergic, or glutamatergic neurotransmitter systems.

Chapter 2

2 Methods

2.1 ADNI Overview

Data used in the preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). All subjects in ADNI undergo both cognitive and clinical assessments and have structural MRIs taken for 2-3 years at pre-scheduled intervals. AD patients undergo a baseline assessment and then an assessment at, 6, 12 and 24 months. MCI patients at high risk for conversion to AD undergo a baseline assessment and then subsequent assessments at 6, 12, 18, 24 and 36 months. Participants from earlier ADNI cohorts were also followed in ADNI2/GO and ADNI3 where they were assessed at baseline enrollment, month 3, month 6, month 12, and annually thereafter. For up-to-date information, see www.adni-info.org.

2.2 Participants

Subjects were selected from the ADNI database and categorized into distinct subgroups based on endorsed symptoms of psychosis as assessed by the Neuropsychiatric Inventory (NPI)[43] or Neuropsychiatric Inventory questionnaire (NPI-Q)[44]. Inclusion criteria for patients endorsing psychotic symptoms included a clinical diagnosis of AD or MCI due to AD, at least one episode of delusions or hallucinations as assessed by either the NPI or NPI-Q delusion and/or hallucination domain scores, an available UCSF volumetric measurement of a 1.5T or 3T MRI scan at or after the first onset of psychosis (delusions/hallucinations), and genome wide analysis data. Inclusion criteria for control participants included a clinical diagnosis of AD, the absence of delusions and hallucinations throughout the course of the ADNI studies, at least three available UCSF volumetric measurement of a 1.5T or 3T MRI scan, and available genome wide analysis data, as of ADNI data available on January 1, 2018. Exclusion criteria for both groups included a history of brain injury, other neurological disorders (ex. Dementia with Lewy Bodies, Parkinson's disease etc.), psychiatric disorders (ex. Schizophrenia, Bipolar

disorder etc.) or strokes, as determined based on clinical assessment, which could account for the presence of delusions and/or hallucinations.

All participants who developed psychotic symptoms were matched as closely as possible with AD patients that did not develop that particular symptom (i.e. hallucinations or delusions) for disease severity using the scores from the Clinical Dementia Rating scale (CDR) global score, sex, age, cognitive ability using the Mini Mental State Exam (MMSE) total score, years of education, number of ApoE4 alleles, and MRI scanner strength. To match the group of participants endorsing symptoms of psychosis with the control group, the range of values of age, education, CDR global score, and MMSE total score for those endorsing symptoms of delusions and/or hallucinations were applied as a filter to the available control group.

2.3 Demographic and Behavioural Data Analysis

Delusion and hallucination domain scores from the Neuropsychiatric Inventory Questionnaire (NPI-Q) and the full Neuropsychiatric Inventory (NPI) were extracted from the ADNI database for participants meeting the inclusion criteria as defined above on January 1, 2018. Phase 1 of ADNI (ADNI-1) used the NPI-Q which provides a binary response (yes or no) to assess the presence or absence of symptoms for each domain. Phase 2 of ADNI (ADNI-GO/2) used the full NPI which allows for the identification of specific subtypes of neuropsychiatric symptoms. Prompts for the delusion domain on the NPI include paranoid ideations such as believing that their life is in danger or that others are stealing from them, and misidentification phenomenon such as believing that their spouse is not who they claim to be. Prompts for the hallucination domain on the NPI include endorsement of abnormal visual, auditory, olfactory, or tactile sensations and/or perceptions in the absence of any external stimuli; for example, hearing voices or seeing things that are not actually present. For participants endorsing psychotic symptoms on multiple visits, data from the first ADNI visit in which psychotic symptoms (delusions/hallucinations) were present were included in the analysis. For the control group, the NPI and NPI-Q scores for all available ADNI visits were reviewed to ensure that participants did not develop delusions and/or hallucinations over their disease course.

2.4 Neuroimaging Data Preprocessing and FreeSurfer Analysis

High resolution anatomical T1weighted images were preprocessed by the Mayo Clinic. Initial preprocessing included a two-step quality assessment procedure. The first step involved assessing adherence to defined ADNI MRI collection protocol. The second preprocessing step involved series-specific quality assessment and included gradient warping, scaling, and correction for image intensity and inhomogenities. Preprocessed ADNI cross-sectional data [UCSFFSX] images were then analyzed by the UCSF ADNI group (Co-I Norbert Schuff) using FreeSurfer version 4.3 for images collected at 1.5T and FreeSurfer version 5.1 for images collected at 3T. Although two different field-strengths were used, FreeSurfer procedures have been shown to have good re-test reliability across field strengths[116,117]. The T1 weighted images were processed and segmented using the 2010 Deskian-Killany atlas and the 2009 Destrieux atlas. Briefly, the processing steps included segmentation of grey matter, white matter and subcortical structures and subsequent cortical parcellation. A visual quality control was performed to assess overall segmentation accuracy[118–129]. It is important to note that cortical thickness estimates have been shown to vary across different versions of FreeSurfer[130], but it has also been shown that within the ADNI cohorts, FreeSurfer version does not affect the reliability of patient classification on diagnostic group (healthy controls, MCI or AD) based on cortical thickness measurements obtained from FreeSurfer[131].

In order to conduct a whole brain analysis, eighty-two cortical and subcortical regions of interest (ROI) from the UCSF FreeSurfer cross-sectional ADNI data analysis were included (Appendix A). Cortical thickness and subcortical volume measurements for the ROIs were extracted. To account for individual variations in brain size, all subcortical volume measurements were adjusted for total intracranial volume (TIV). This was done since prior literature suggests that volume but not cortical thickness measurements are highly correlated with TIV [132–134]. MRI data was only included if it passed or partially passed regional image segmentation quality assessment of the frontal, temporal, occipital and basal ganglia regions. For subsequent statistical analyses, volume and cortical

thickness measurements were adjusted for sex, age, years of education, CDR global score, MMSE total scores, either through regression models or by including these variables as covariates. All cortical and subcortical measurements were also transformed into z-scores before further analyses.

2.5 Genetic Data Acquisition and Preprocessing

DNA information was derived from one of two sources: 1) peripheral blood, or 2) immortalized lymphocyte cell lines. ADNI-1 participants were genotyped using the Illumina Human610-Quad BeadChip (Illumina, Inc. San Diego, CA). All genotyping and initial preprocessing was conducted by the ADNI Genetics Core group. Further details on genotyping methods and preprocessing have been outlined by the ADNI Genetics Core group [135]. Initial quality control (QC) and imputation was performed by Sejal Patel and the lab of Dr. Jo Knight at the University of Toronto. Genotype imputation is a procedure whereby unsequenced SNPs are inferred based on directly sequenced SNPs. This procedure works on the premise that groups of SNPs are likely to be inherited together (haplotypes). SNPs that have been sequenced act as markers which are then compared to the haplotypes of individuals in a reference panel (ex. HapMap). Regions of shared genotypes between the sequenced individuals and the reference panel are then identified. The reference panel is then used to infer unsequenced genotypes for SNPs that were not directly sequenced[136].

QC was performed on the ADNI1 GWAS data (N=757) using PLINK (version 1.07, Purcell et al., 2007). Individuals with discordant sex information (when samples are incorrectly marked as male or female based on ascertained sex), high level of missing data (> 2%) and heterozygosity rates greater than three standard deviations from the mean were removed from the sample. One of each pair of individuals displaying a high level of pair-wise identity by descent (IBD > 0.185) were also removed. In addition, SNPs with minor allele frequency (MAF) <1% and Hardy-Weinberg equilibrium ($p < 1x10^{-7}$) were removed. After QC, 662 individuals remained in the analysis set. Multidimensional scaling (MDS) was performed in PLINK using HapMap3[138] as a reference panel. When the population was compared with the CEU (CEPH - Utah residents with ancestry from

northern and western Europe), YRI (Yoruba in Ibadan, Nigeria), JPT (Japanese in Tokyo, Japan), TSI (Tuscans in Italy) and CHB (Han Chinese in Beijing, China) ancestry, the sample clustered around CEU and TSI sample. MDS was subsequently carried out with the ADNI1, CEU, TSI and Jewish ancestry samples and aligned completely with the later three samples. The ADNI1 dataset was imputed using 1000 Genomes Phase I integrated variant set (March 2012). Given the small sample size of participants that were of non-Hispanic Caucasian ethnicity, these individuals were removed prior to subsequent analysis to control for any confounding effects. From the preprocessed data, we then selected only participants meeting the inclusion criteria defined above.

2.6 Candidate SNP Selection

After conducting a thorough review of the literature, we identified SNPs with known functional consequences and associations with neuropsychiatric symptoms, focusing in particular on SNPs in the following genes in the cholinergic system: BCHE, ACHE, CHRNA7, CHRNA4, CHRNB2; and in the following genes in the dopaminergic system: COMT, DRD1, DRD2, DRD3; and in the glutamatergic system: GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A. Concluding our review, we selected 15 candidate SNPs to include (Table 1,2). Given that there is limited literature on SNPs in neurotransmitter systems that may be associated with psychosis in AD, the SNPs that we selected have previously been reported to be implicated in the development of psychotic symptoms in other neurodegenerative or psychiatric disorders, associated with AD, and/or to have functional consequences on transcript or protein levels. SNP data were recoded into disjunctive format prior to additional analyses. Using this format, each SNP was treated as a categorical variable with three levels (i.e. homozygous dominant, heterozygous, homozygous recessive). The advantages of coding SNPs using this genotypic model have been outlined previously in Beaton, Dunlop, & Abdi (2015)[139], and include being able to assess the contribution of different alleles and genotypes to observed phenotypic traits or behaviours. This is particularly important because the minor or major allele coding scheme is often subjective and based on a particular cohort of participants. As such, what is coded as the major or minor allele in one study may vary across studies with different samples of participants. Using the genotypic model therefore

allows us to treat each genotype as a categorical variable and investigate the unique contribution of each genotype using a more general approach. To ensure that we were sufficiently powered to assess the effects of different alleles/genotypes, homozygous recessive genotypes with frequencies < 5%, were combined with heterozygous genotypes to form one category (?a). This second grouping encompassed individuals with both the homozygous recessive genotype (aa) and the heterozygous genotype (Aa).

Table 1. Candidate single nucleotide polymorphisms (SNPs) in the Cholinergic (BCHE, CHRNA7) and the Dopaminergic (COMT, DRD1, DRD2, DRD3) neurotransmitter systems.

Gene	Chromosome	SNP	Literature Summary	Key Findings
Butyrylcholinesterase (BCHE)	3	rs1803274	Darvesh, Hopkins & Geula., (2003)[140] Yoo et al., (2014)[141]	• BCHE – K variant has reduced catalytic activity, about 30% of the usual BChE • BCHE-K protects against pathology of AD that affects frontal cortical thickness and neuropsychiatric symptoms
Cholinergic Receptor, Nicotinic Alpha 7 Subunit (CHRNA7)	15	rs6494223	Carson et al., (2008)[100]	• Frequency of delusional symptoms was higher in patients homozygous for the T allele compared to the CC or CT genotypes
Catechol-O-Methyltransferase (COMT)	22	rs4680	Rosa et al., (2004)[142]	• Val carriers have high enzyme activity, may have reduced dopamine levels in the prefrontal cortex, leading to decrease in D1 receptors activation • Can lead to impairment in working memory
Dopamine Receptor D1 (DRD1)	5	rs686	Huang et al., (2008)[143]	• G allele of rs686 decreases the levels of DRD1 expression by inhibiting the binding of microRNA miR-504 to the DRD1 3′-UTR
Dopamine Receptor D2 (DRD2)	11	rs6277	Duan et al., (2003)[144]	• Reported 50% of the time, 957C>T, decreased DRD2 mRNA stability and translation and reduced dopamine-induced-up-regulation of DRD2 membrane expression in vitro • Alters the folding of the mRNA, mRNA is less stable which leads to markedly reduced protein synthesis rates
Dopamine Receptor D2 (DRD2)	11	rs1076560	Bertolino et al., (2009)[145]	• Intronic SNP rs1076560 strongly associated with D2 short isoform/D2 long isoform ratios with GG schizophrenia subjects showing a higher percentage of the D2 short

				isoform mRNA in prefrontal cortex than GT subjects
Dopamine Receptor D2 (DRD2)	11	rs1800497	Makoff et al., (2000)[146]	• C allele is a risk factor for hallucinations. This finding was found to be clinically significant in context of advanced neurodegeneration of chronic PD
Dopamine Receptor D3 (DRD3)	3	rs6280	Savitz et al., (2013)[147]	• Only known polymorphism that alters protein structure in this gene • Glycine allele yields D3 autoreceptors that have a higher affinity for DA and display more robust intracellular signaling

Table 2. Candidate single nucleotide polymorphisms (SNPs) in the Glutamatergic (GRIN2A, GRIN2B, GRIN3A, GRIN3B) neurotransmitter system.

Gene	Chromosome	SNP	Literature Summary	Key Findings
Glutamate Ionotropic Receptor NMDA Type Subunit 2A (GRIN2A)	16	rs9922678	Schizophrenia Working Group., (2014)[148]	• Minor homozygote associated with the development of schizophrenia (OR=1.06)
Glutamate Ionotropic Receptor NMDA Type Subunit 2B (GRIN2B)	12	rs1805502	Weickert et al., (2013)[149]	• NR1 and NR2C mRNA decreased in post-mortem brain analysis of those with schizophrenia • Found that the expression of NR1 subunit mRNA was significantly reduced in patients with schizophrenia who were C carriers of the SNP rs1805502 when compared to heterozygous controls (p =.008)
Glutamate Ionotropic Receptor NMDA Type Subunit 2B (GRIN2B)	12	rs1806201	Andreoli et al., (2014)[150]	• Significant contribution from the GRIN2B rs1806201 T allele towards Alzheimer's disease susceptibility (adjusted odds ratio (OR=1.92, (95%CI: 1.40–2.63))
Glutamate Ionotropic Receptor NMDA Type Subunit 2B (GRIN2B)	12	rs10845840	Stein et al., (2010)[115]	• Risk alleles for lower temporal lobe volume at this SNP were significantly over-represented in AD and MCI subjects versus controls (OR=1.27; p =.039)
Glutamate Ionotropic Receptor NMDA Type Subunit 3A (GRIN3A)	9	rs3739722	Liu et al., (2009)[151]	• Genetic variation of the NR3A, but not NR3B, subunit of the NMDA receptor may be a risk factor for AD pathogenesis among the Taiwanese population
Glutamate Ionotropic Receptor NMDA Type Subunit 3A (GRIN3A)	9	rs10989591	Gallinat et al., (2007)[152]	• T,T individuals appeared to show better prefrontal information processing (higher frontal P300 amplitudes), could reflect higher NMDA receptor efficacy
Glutamate Ionotropic Receptor NMDA Type Subunit 3B (GRIN3B/ABCA7 -in linkage disequilibrium with GRIN3B)	19	rs3764650	Karch et al., (2012)[153]	• Minor allele associated with a later age of AD onset and shorter disease course

2.7 Statistical Analysis

Independent samples t-tests were used to compare age, years of education, MMSE total score and CDR global score for participants endorsing psychotic symptoms of interest and control groups. For the comparison of multiple cohorts of participants with psychotic symptoms, a Kruskal-Wallis test was used to determine group differences. Chi-square tests were used to compare the two groups on sex distribution, number of ApoE4 alleles, and scanner strength (1.5T vs. 3T).

2.7.1 Partial Least Squares Correspondence Analysis: Overview

Partial least squares correspondence analysis (PLS-CA) is a multivariate analysis technique that is both a generalization of partial-least squares correlation (used in neuroimaging studies) and an extension of correspondence analysis (dimension reduction technique for categorical variables). This method was formalized by Beaton and colleagues and is extensively detailed in their paper [139]. To summarize, unlike traditional PLS, PLS-CA is able to simultaneously analyze two data sets that contain both continuous (i.e. neuroimaging) and categorical (i.e. genetic) variables. This process works through transforming continuous variables, like cortical thickness and subcortical volume measurements, into pseudo-categorical variables using an Escofier transformation. PLS-CA uses generalized singular value decomposition to identify orthogonal pairs of underlying latent variables, with the first extracted pair explaining the greatest amount of covariance in the data sets. Non-parametric inferencing methods such as permutation and bootstrap resampling techniques are used to identify significant and stable components. With bootstrap confidence intervals, in particular, allowing for the post-hoc identification of group level differences. In addition, through the use of PLS-CA, we are able to treat SNPs as categorical variables, instead of as numeric based on the frequency of either the minor or major allele, thereby allowing us to examine how different SNP genotypes contribute to different effects within our sample. Overall, the PLS-CA approach can be used to identify global level interactions. These interactions can be inferred based on the latent factor and variable plots for each component. More specifically, ROIs and

genotypes that are in the same direction as one another, on the same component, can be inferred to be interacting together.

2.7.2 PLS-CA

Three independent PLS-CA were conducted to identify neuroanatomical and genetic correlates of delusions and hallucinations. The rationale behind separating the analyses into three different parts was to more closely examine the neuroanatomical and genetic interactions with increased power resulting from a larger sample size. This was achieved by first using a binary categorization scheme to identify interactions associated with the presence vs. absence of delusions and subsequently the neuroanatomical and genetic interactions associated with the presence vs. absence of hallucinations. The final analysis, which combined both of the aforementioned cohorts, was conducted to identify and parse any *differences* in neuroanatomical and genetic interactions for those with symptoms of hallucinations, delusions or both. 82 ROIs and 15 SNPs were included in the analysis. All cortical thickness and subcortical volume measurements were adjusted for participant age, sex, years of education, MMSE total score, CDR global score, number of ApoE4 alleles, and scanner strength. To account for inter-individual differences in brain size, all subcortical volumes were also adjusted for total intracranial volume. Significance of each component was tested using 1000 permutations ($p < 0.05$). Significance of the variables contributing to each component was assessed using 1000 bootstrapped samples (bootstrap ratio > 2.0). Three different PLS-CA analyses were conducted with the subgroups categorized as follows:

Analysis 1: Delusion Cohort (Binary Categorization). The first analysis categorized patients with AD/MCI into two groups based on the presence or absence of symptoms of delusions, irrespective of any other neuropsychiatric symptom. The two groups were categorized as follows: 1) AD patients who never endorsed symptoms of delusions throughout the duration of their ADNI visits (AD-D), and 2) AD or MCI patients who endorsed symptoms of delusions at their baseline ADNI visit or who developed symptoms of delusions over their disease course (AD+D)

Analysis 2: Hallucination Cohort (Binary Categorization). The second analysis categorized patients with AD/MCI into two groups based on the presence or absence of hallucinations, irrespective of any other neuropsychiatric symptom. The two groups were categorized as follows: 1) AD or MCI patients who never endorsed symptoms of hallucinations throughout the duration of their ADNI visits (AD – H), and 2) AD or MCI patients who endorsed symptoms of hallucinations at their baseline ADNI visit or who developed symptoms of hallucinations over their disease course (AD+H).

Analysis 3: Combined Cohort (4 groups – to directly compare the interactions between brain regions and SNPs in those with AD+D, AD+H, AD+DH and AD-DH). The final analysis aggregated all patients with AD/MCI that had symptoms of hallucinations and delusions, or the absence of these symptoms, into one analysis. In this analysis, patients were categorized into four distinct groups: 1) AD patients who never endorsed symptoms of delusions or hallucinations throughout the duration of their ADNI visits (AD-DH); 2) AD or MCI patients who endorsed only symptoms of hallucinations at their baseline ADNI visit or who developed symptoms of hallucinations over their disease course (AD+H); 3) AD or MCI patients who endorsed only symptoms of delusions at their baseline ADNI visit or who developed symptoms of delusions over their disease course (AD+D), and 4) patients who endorsed symptoms of both delusions and hallucinations (AD+DH), at the identified ADNI visit.

PLS-CA was conducted using R (Version 3.5.2) and the related statistic packages, ExPosition and TExPosition (Beaton, Chin Fatt, & Abdi 2014; Beaton, Rieck, Fatt, & Abdi, 2013), using the pipeline proposed in Beaton et al., 2015.

2.7.3 Principal Component Analysis and Binary Logistic Regression

To cross-validate brain regions identified by the PLS-CA, binary logistic regression analyses for all participants with available imaging data (irrespective of GWAS availability) were run for both the hallucination and delusion cohorts. Principal component analysis (PCA) with varimax rotation and Kaiser normalization was used as a dimension reduction technique to reduce the 82 ROIs into components. All cortical thickness and subcortical volumes for each ROI were transformed into Z-scores across

subjects prior to running the PCA. Following the PCA, the rotated component matrix was inspected and any components that did not have any ROIs that loaded most strongly to a particular component were excluded. The component scores for each retained component were then entered into binary logistic regression models with the dependent variable being either the presence/absence of delusions or the presence/absence of hallucinations. Additional covariates in the model included age, years of education, sex, CDR global score, MMSE total score, number of ApoE4 alleles and MRI scanner strength. Follow-up logistic regression models were run by removing any variables that were not significant in the prior model. Given the high degree of multicollinearity between ROIs in the identified components, post-hoc analysis of covariance (ANCOVA) with FDR correction was used to identify specific ROIs that may be contributing to the presence of hallucinations/delusions.

PCA, binary logistic regression and post-hoc ANCOVAs were conducted using IBM SPSS Statistics for Mac, Version 25.0.

Chapter 3

3 Results

3.1 Imaging and Genetics: PLS-CA Results

3.1.1 Delusion Cohort

A total of 188 participants were identified from the ADNI-1 database as meeting the inclusion criteria. Of these, n=66 endorsed symptoms of delusions (AD+D), and n=122 did not endorse symptoms of delusions (AD-D). Independent samples t-test comparing age, years of education, CDR global score, and MMSE total score, did not identify any significant differences between the two groups. Additional chi-square tests did not identify any group differences in sex distribution, MRI field strength, or number of ApoE4 alleles (Table 3). The minor allele frequencies for the 15 SNPs of interest were calculated for the entire cohort and are reported in Table 4.

Results of the PLS-CA did not identify any significant differences in interactions between ROIs and SNPs that separated those with delusions from those without (Omnibus: $p_{perm} = .118$, Component 1: $p_{perm} = .161$). Despite not reaching the threshold for significance, Component 1 explained 40.45% of the variance in the dataset (Figure 1A). Although not significant, the interaction of specific ROIs and SNPs that are more closely associated with the delusion cohort, are ROIs with cortical thickness values below the grand mean (ROIs below the horizontal axis in Figure 1B, see Table 5 for complete list of ROIs) and SNPs that are to the left of the vertical axis in Figure 1B.

Table 3. PLS-CA Delusion Cohort: Demographic and disease profile.

	Delusions (AD+D) N = 66		**No Delusions (AD-D) N = 122**			
	Mean	*(SD)*	Mean	*(SD)*	*t*	*p-value*
Age	75.94	*6.6*	76.07	*7.1*	0.1	.91
Years of Education	15.18	*2.9*	15.16	*3.1*	-0.06	.96
CDR Global Score	0.88	*0.43*	0.92	*0.43*	0.7	.51
MMSE Total Score	22.67	*4.5*	21.47	*4.3*	-1.8	.075
	Males	*Females*	*Males*	*Females*	*Fischer's Exact Test (2-sided)*	
Sex (%)	53.0	47.0	62.3	37.7	0.277	
MRI Field Strength	*1.5T*	*3T*	*1.5T*	*3T*	*Fischer's Exact Test (2-sided)*	
	64	2	119	3	1.00	

	Delusions (AD+D)			**No Delusions (AD-D)**			
Number of ApoE4 alleles	*0*	*1*	*2*	*0*	*1*	*2*	*Pearson Chi-Square*
	22	31	13	41	58	23	.99

Table 4. PLS-CA - Delusion Cohort. Minor allele frequencies for the 15 SNPs of interest

Delusion Cohort PLS-CA, N=188			
Gene	**SNP**	**Minor Allele**	**Minor Allele Frequency**
BCHE	rs1803274	T	0.170
CHRNA7	rs6494223	T	0.402
COMT	rs4680	A	0.484
DRD1	rs686	G	0.359
DRD2	rs1076560	A	0.830
DRD2	rs1800497	A	0.221
DRD2	rs6277	G	0.431
DRD3	rs6280	C	0.370
GRIN2A	rs9922678	A	0.330
GRIN2B	rs10845840	T	0.492
GRIN2B	rs1805502	G	0.156
GRIN2B	rs1806201	A	0.338
GRIN3A	rs10989591	T	0.293
GRIN3A	rs3739722	T	0.100
GRIN3B	rs3764650	G	0.080

Figure 1A.

Delusion Cohort Omnibus p-value: .118	
Component	**P-value**
1	0.16
2	0.67
3	0.38
4	0.13
5	0.64

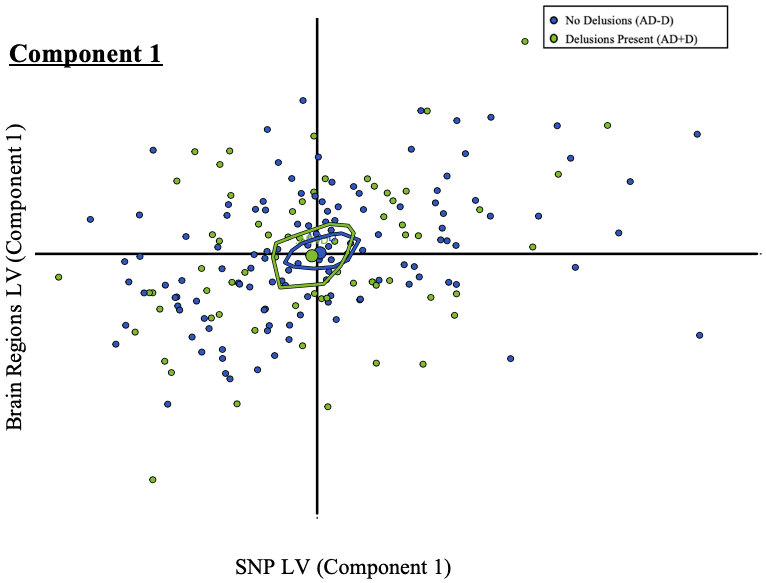

Figure 1B.

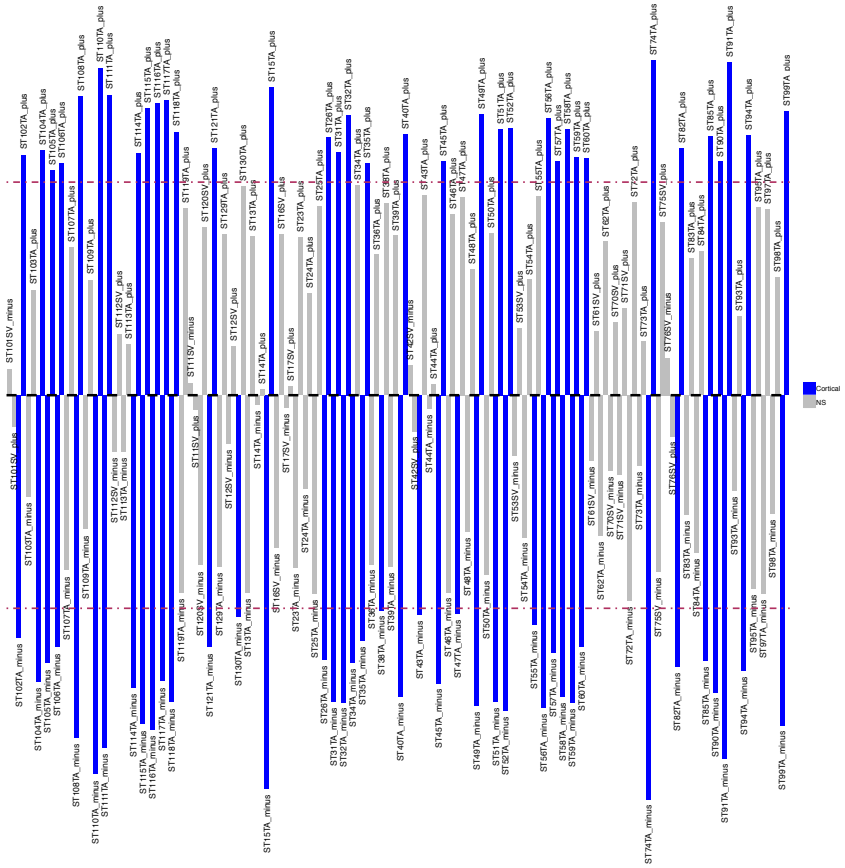

Figure 1C.

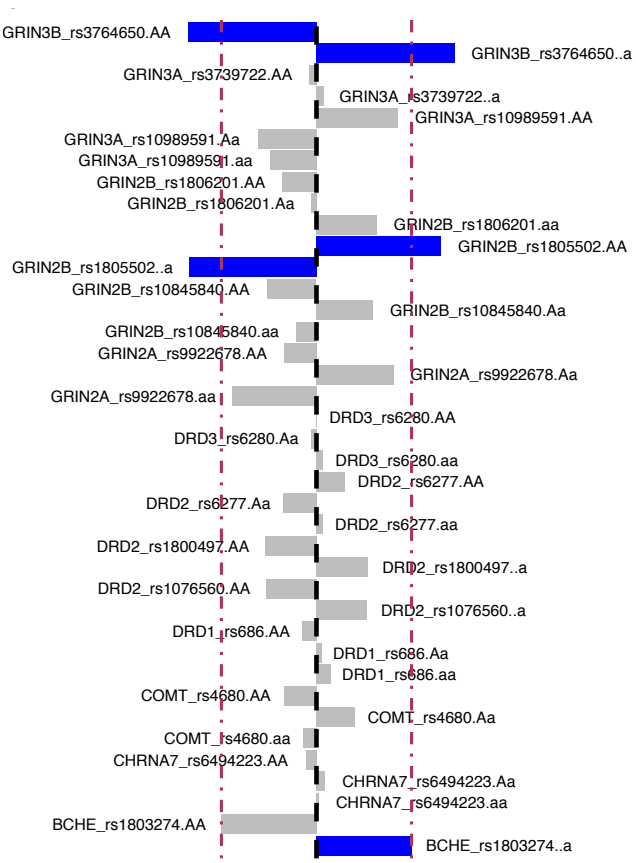

Figure 1. Delusion Cohort PLS-CA results. **A.** Component p-values and latent variable (LV) plot for Component 1. The horizontal axis represents the SNPs and the vertical axis represents the brain regions of interest. Ellipsoids indicate boot-strap confidence intervals (95%) **B.** Neuroimaging boot-strap regression results for Component 1 with blue bars indicating significant brain regions. Red dashed line indicates the threshold for significance (+2 and -2) **C.** Single nucleotide polymorphisms boot-strap regression results for Component 1 with blue bars indicating significant SNPs.

Table 5. Delusion Cohort: Neuroimaging boot-strap regression, summary of ROIs with cortical thickness values below the grand mean for Component 1.

Delusion Cohort - ROIs more closely associated with the delusion cohort for Component 1	
ST102TA_RightParacentral	ST40TA_LeftMiddleTemporal
ST102TA_RightParacentral	ST43TA_LeftParacentral
ST105TA_RightParsOrbitalis	ST45TA_LeftParsOpercularis
ST106TA_RightParsTriangularis	ST47TA_LeftParsTriangularis
ST108TA_RightPostCentral	ST49TA_LeftPostCentral
ST110TA_RightPrecentral	ST51TA_LeftPrecentral
ST111TA_RightPrecuneus	ST52TA_LeftPrecuneus
ST114TA_RightRostralMiddleFrontal	ST55TA_LeftRostralMiddleFrontal
ST115TA_RightSuperiorFrontal	ST56TA_LeftSuperiorFrontal
ST116TA_RightSuperiorParietal	ST57TA_LeftSuperiorParietal
ST117TA_RightSuperiorTemporal	ST58TA_LeftSuperiorTemporal
ST118TA_RightSupramarginal	ST59TA_LeftSupramarginal
ST121TA_RightTransverseTemporal	ST60TA_LeftTemporalPole
ST130TA_RightInsula	ST74TA_RightCaudalMiddleFrontal
ST15TA_LeftCaudalMiddleFrontal	ST82TA_RightCuneus
ST26TA_LeftFusiform	ST85TA_RightFusiform
ST31TA_LeftInferiorParietal	ST90TA_RightInferiorParietal
ST32TA_LeftInferiorTemporal	ST91TA_RightInferiorTemporal
ST34TA_LeftIsthmusCingulate	ST94TA_RightLateralOccipital
ST35TA_LeftLateralOccipital	ST99TA_RightMiddleTemporal
ST38TA_LeftLingual	

3.1.2 Hallucination Cohort

A total of 117 participants were identified from the ADNI-1 database as meeting the inclusion criteria. Of these, n=36 endorsed symptoms of hallucinations (AD+H), and n=81 did not endorse symptoms of hallucinations (AD-H). Independent samples t-test comparing age, years of education, CDR global score, and MMSE total score, did not identify any significant differences between the two groups. Additional chi-square tests did not identify any group differences in sex distribution, MRI field strength, or number of ApoE4 alleles (Table 6). The minor allele frequencies for the 15 SNPs of interest were calculated for the entire cohort and are reported in Table 7.

Results of the PLS-CA identified a trend towards significance for Component 1, with the interaction of ROIs and SNPs in Component 1 explaining 45.44% of the variance in the dataset (Omnibus: $p_{perm} = .049$, Component 1: $p_{perm} = .059$; Figure 2A). Boot strap analysis showed that cortical thickness and subcortical volumes below the grand mean for bilateral frontal regions, bilateral cingulate regions, bilateral temporal regions, bilateral fusiform, right entorhinal, left inferior parietal, right lingual, right precuneus, right insula, and right accumbens area (Figure 2B; see Table 8 for complete list of ROIs) were associated with the major homozygote of rs3764650 in GRIN3B, and the minor homozygote of rs9922678 in GRIN2A (Figure 2C).This pattern of brain structure and combination of SNPs was more closely associated with those with symptoms of hallucinations when compared to those without.

Table 6. PLS-CA Hallucination Cohort: Demographic and disease profile

	Hallucinations (AD+H) N = 36		**No Hallucinations (AD-H) N = 81**			
	Mean	*(SD)*	Mean	*(SD)*	*t*	*p-value*
Age	74.89	*7.1*	75.85	*6.2*	.74	.46
Years of Education	14.56	*3.1*	15.44	*2.9*	1.5	.14
CDR Global Score	1.28	*0.61*	1.12	*0.33*	-1.42	.16
MMSE Total Score	20.22	*5.4*	20.77	*4.4*	.57	.57
	Males	*Females*	*Males*	*Females*	*Fischer's Exact Test (2-sided)*	
Sex (%)	52.8	47.2	58.0	42.0	0.687	
MRI Field Strength	*1.5T*	*3T*	*1.5T*	*3T*	*Fischer's Exact Test (2-sided)*	
	36	0	78	3	0.552	
	Hallucinations (AD+H)			**No Hallucinations (AD-H)**		
Number of ApoE4 alleles	*0*	*1*	*2*	*0*	*1*	*2*	*Pearson Chi-Square*
	10	21	5	25	39	17	.54

Table 7. PLS-CA - Hallucination Cohort. Minor allele frequencies for the 15 SNPs of interest.

Hallucination Cohort N = 117			
Gene	**SNP**	**Minor Allele**	**Minor Allele Frequency**
BCHE	rs1803274	T	0.171
CHRNA7	rs6494223	T	0.427
COMT	rs4680	A	0.483
DRD1	rs686	G	0.371
DRD2	rs1076560	A	0.171
DRD2	rs1800497	A	0.235
DRD2	rs6277	G	0.432
DRD3	rs6280	C	0.346
GRIN2A	rs9922678	A	0.329
GRIN2B	rs10845840	C	0.470
GRIN2B	rs1805502	G	0.141
GRIN2B	rs1806201	A	0.350
GRIN3A	rs10989591	T	0.303
GRIN3A	rs3739722	T	0.120
GRIN3B	rs3764650	G	0.081

Figure 2A.

Hallucination Cohort Omnibus p-value: .049	
Component	**P-value**
1	0.06
2	0.20
3	0.17
4	0.43
5	0.17

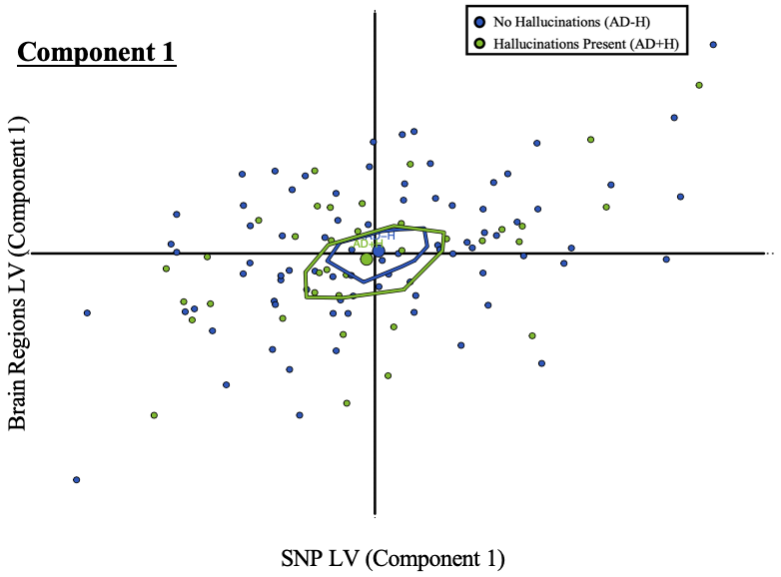

Figure 2B.

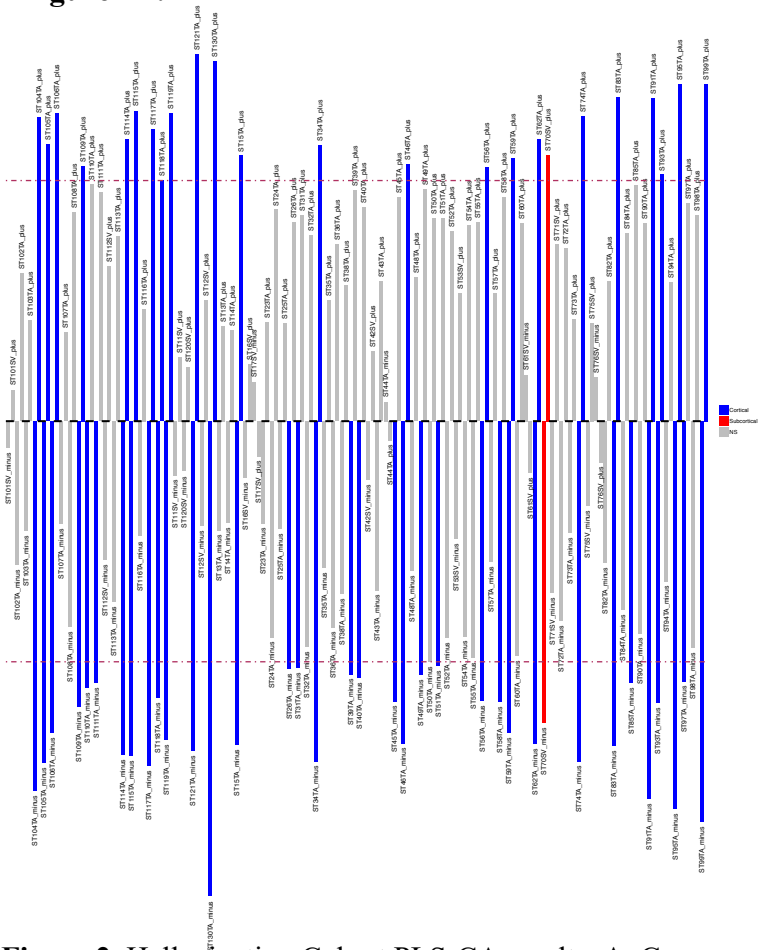

Figure 2C.

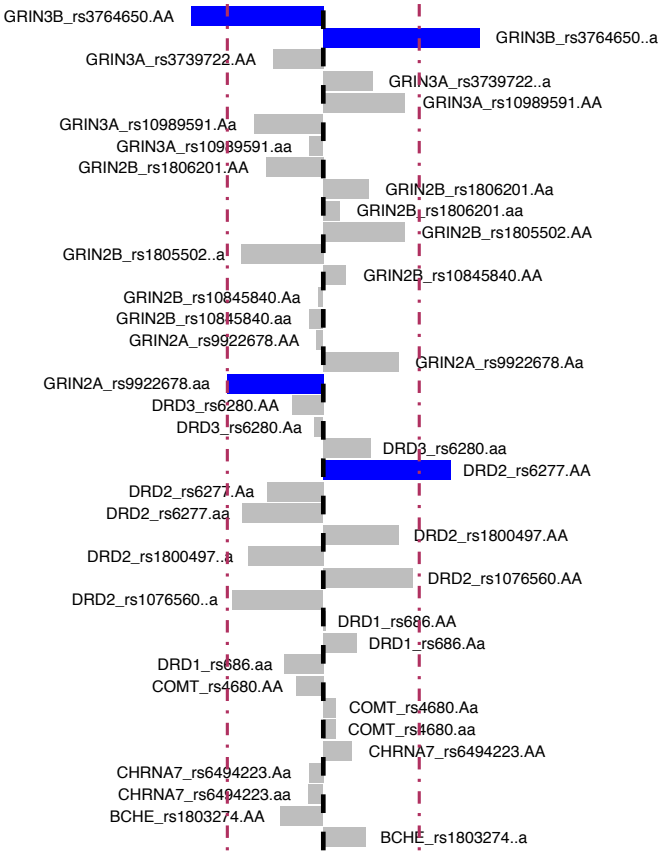

Figure 2. Hallucination Cohort PLS-CA results. **A.** Component p-values and latent variable (LV) plot for Component 1. The horizontal axis represents the SNPs and the vertical axis represents the brain regions of interest. Ellipsoids indicate boot-strap confidence intervals (95%) **B.** Neuroimaging boot-strap regression results for Component 1 with blue bars indicating significant cortical regions and red bars indicating significant subcortical regions. Red dashed line indicates the threshold for significance (+2 and -2) **C.** Single nucleotide polymorphisms boot-strap regression results for Component 1 with blue bars indicating significant SNPs.

Table 8. Hallucination Cohort: Neuroimaging boot-strap regression, summary of significant ROIs with cortical thickness values below the grand mean for Component 1.

Hallucination Cohort - Significant ROIs with cortical thickness and subcortical volumes below the grand mean.	
ST104TA_RightParsOpercularis	ST45TA_LeftParsOpercularis
ST105TA_RightParsOrbitalis	ST46TA_LeftParsOrbitalis
ST106TA_RightParsTriangularis	ST49TA_LeftPostCentral
ST109TA_RightPosteriorCingulate	ST51TA_LeftPrecentral
ST110TA_RightPrecentral	ST56TA_LeftSuperiorFrontal
ST111TA_RightPrecuneus	ST58TA_LeftSuperiorTemporal
ST114TA_RightRostralMiddleFrontal	ST59TA_LeftSupramarginal
ST15TA_LeftCaudalMiddleFrontal	ST62TA_LeftTransverseTemporal
ST117TA_RightSuperiorTemporal	ST74TA_RightCaudalMiddleFrontal
ST118TA_RightSupramarginal	ST83TA_RightEntorhinal
ST119TA_RightTemporalPole	ST85TA_RightFusiform
ST121TA_RightTransverseTemporal	ST91TA_RightInferiorTemporal
ST130TA_RightInsula	ST93TA_RightIsthmusCingulate
ST15TA_LeftCaudalMiddleFrontal	ST95TA_RightLateralOrbitofrontal
ST26TA_LeftFusiform	ST97TA_RightLingual
ST31TA_LeftInferiorParietal	ST99TA_RightMiddleTemporal
ST34TA_LeftIsthmusCingulate	ST70SV_RightAccumbensArea
ST39TA_LeftMedialOrbitofrontal	
ST40TA_LeftMiddleTemporal	

3.1.3 Combined Cohort

A total of 207 participants were identified from the ADNI-1 database as meeting the inclusion criteria. Of these, n=21 endorsed symptoms of hallucinations only (AD+H), n=54 endorsed symptoms of delusions only (AD+D), n=10 endorsed symptoms of both hallucinations and delusions (AD+DH), and n=116 did not endorse symptoms of hallucinations (AD-H). A Kruskal-Wallis test with Bonferroni correction of between group differences identified a significant difference in CDR global score between the groups, with the AD+H group having on average a greater CDR score (higher disease severity) than the AD+D group (p=.017). A significant difference was also identified for MMSE total scores, with the AD+H group having on average lower total scores on the MMSE than the AD+D group (p=.022). No significant between group differences were identified for the other cohorts of interest (Table 9). The minor allele frequencies for the 15 SNPs of interest were calculated for the entire cohort and are reported in Table 10.

Results of the PLS-CA identified a trend towards significance for Component 1 (Omnibus: $p_{perm} = .057$, Component 1: $p_{perm} = .071$; Figure 3A), with the interaction of ROIs and SNPs in Component 1 explaining 44.16% of the variance in the dataset. (Figure 3A). Boot strap analysis showed that cortical thickness values below the grand mean for a number of bilateral frontal regions, bilateral temporal regions, bilateral parietal regions, bilateral fusiform, right entorhinal, left isthmus cingulate, left posterior cingulate, bilateral precuneus, right cuneus, left lingual, bilateral lateral occipital, and bilateral insula (Figure 3B; see Table 11 for complete list of ROIs), were associated with the major homozygotes of rs3764650 in GRIN3B and rs1803274 in BCHE, the minor homozygote/heterozygote of rs1805502 in GRIN2B, and with the minor homozygote of rs9922678 in GRIN2A (Figure 3C). This pattern of brain structure and combination of genotypes was more closely associated with the AD+DH group than with any other group. In contrast, cortical thickness values above the grand mean for the aforementioned ROIs were more closely associated with the major homozygote of rs1805502 in GRIN2B, the minor homozygote/heterozygote of rs3764650 in GRIN3B, and the minor homozygote/heterozygote of rs1803274 in BCHE. Moreover, this pattern of brain structure and combination of genotypes was more closely associated with the AD+H group than with any other group.

Table 9. PLS-CA Combined Cohort: Demographic and disease profile

	No Psychosis (AD-DH) N = 116		**Hallucinations Only (AD+H) N = 21**		**Delusions Only (AD+D) N = 54**		**Hallucinations and Delusions (AD+DH) N = 10**			
	Mean	*(SD)*	Mean	*(SD)*	Mean	*(SD)*	Mean	*(SD)*	*t*	Kruskal-Wallis Test: p-value
Age	76.25	*7.0*	75.19	*6.7*	75.94	*6.9*	75.10	*5.7*	0.62	0.892
Years of Education	15.24	*3.0*	14.86	*3.3*	15.57	*2.8*	13.70	*3.0*	3.54	0.316
CDR Global Score	0.89	*0.4*	1.29	*0.7*	0.80	*0.3*	1.30	*0.6*	13.30	0.004
MMSE Total Score	22.09	*4.1*	19.52	*5.7*	23.19	*4.4*	20.20	*5.0*	10.46	0.015
	Males	Females	Males	Females	Males	Females	Males	Females	Pearson Chi-Square (2-sided)	
Sex (%)	61.2	38.8	61.9	38.1	55.6	44.4	40.0	60.0	0.562	
MRI Field Strength	1.5T	3T	1.5T	3T	1.5T	3T	1.5T	3T	Pearson Chi-Square (2-sided)	
	114	2	21	0	52	2	10	0	0.686	

	No Psychosis (AD-DH)			Hallucinations Only (AD+H)			Delusions Only (AD+D)			Hallucinations and Delusions (AD+DH)			
Number of ApoE4 alleles	0	1	2	0	1	2	0	1	2	0	1	2	Pearson Chi-Square
	39	53	24	5	14	2	19	26	9	3	4	3	.623

Table 10. PLS-CA - Combined Cohort. Minor allele frequencies for the 15 SNPs of interest

Combined Cohort PLS-CA, N=201			
Gene	**SNP**	**Minor Allele**	**Minor Allele Frequency**
BCHE	rs1803274	T	0.177
CHRNA7	rs6494223	T	0.415
COMT	rs4680	A	0.485
DRD1	rs686	G	0.363
DRD2	rs1076560	A	0.167
DRD2	rs1800497	A	0.213
DRD2	rs6277	G	0.430
DRD3	rs6280	C	0.356
GRIN2A	rs9922678	A	0.324
GRIN2B	rs10845840	C	0.495
GRIN2B	rs1805502	G	0.152
GRIN2B	rs1806201	A	0.326
GRIN3A	rs10989591	T	0.286
GRIN3A	rs3739722	T	0.102
GRIN3B	rs3764650	G	0.090

Figure 3A.

Combined Cohort Omnibus p-value: .057	
Component	**P-value**
1	0.07
2	0.63
3	0.33
4	0.39
5	0.81

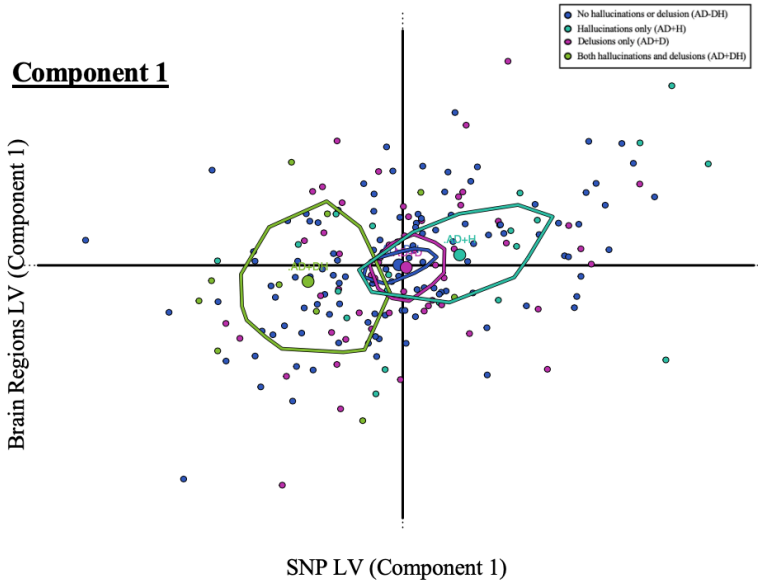

Figure 3B.

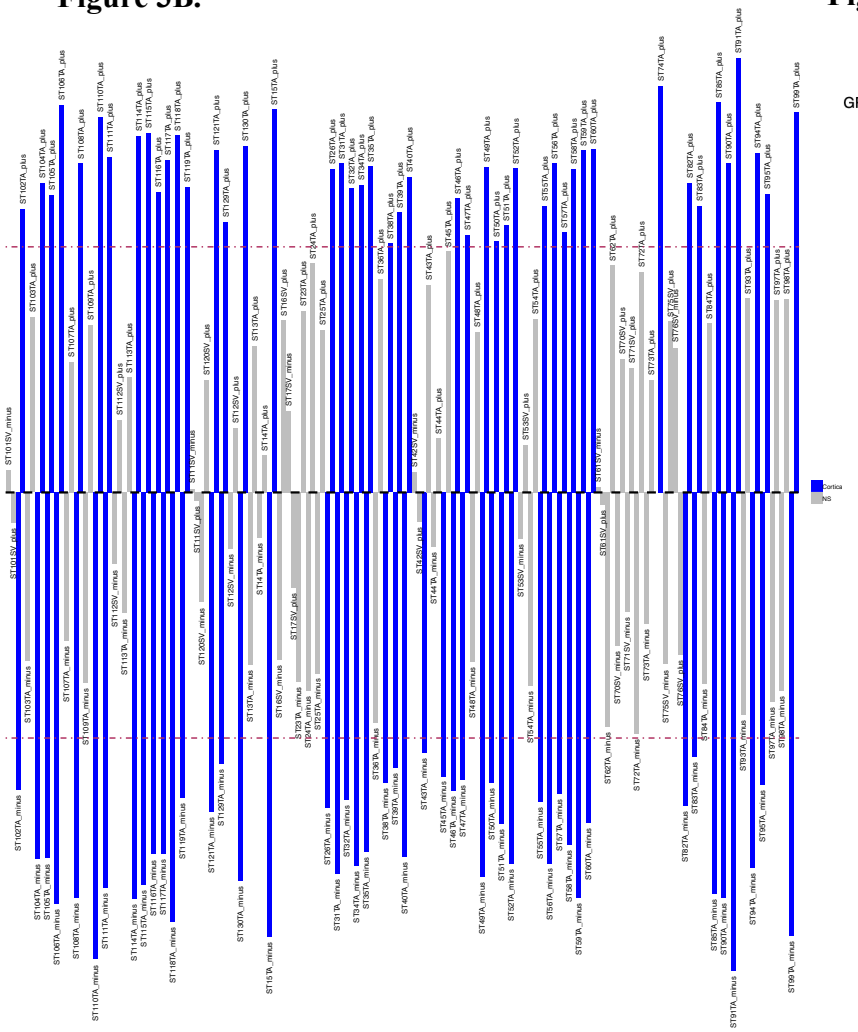

Figure 3C.

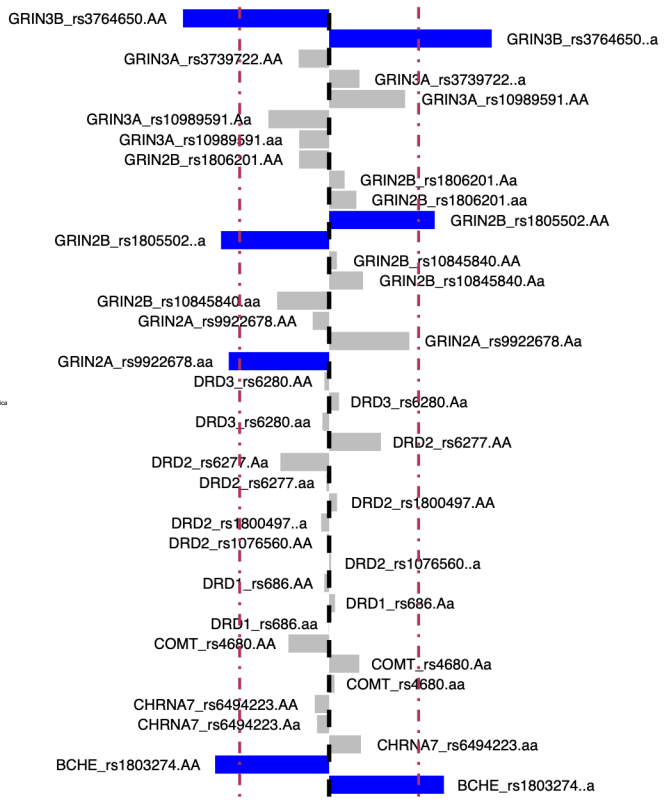

Figure 3. Combined Cohort PLS-CA results. **A.** Component p-values and latent variable (LV) plot for Component 1. The horizontal axis represents the SNPs and the vertical axis represents the brain regions of interest. Ellipsoids indicate boot-strap confidence intervals (95%) **B.** Neuroimaging boot-strap regression results for Component 1 with blue bars indicating significant brain regions. Red dashed line indicates the threshold for significance (+2 and -2) **C.** Single nucleotide polymorphisms boot-strap regression results for Component 1 with blue bars indicating significant SNPs.

Table 11. Combined Cohort: Neuroimaging boot-strap regression, summary of significant ROIs with cortical thickness values below the grand mean for Component 1.

Combined Cohort - Significant ROIs with cortical thickness values below the grand mean	
ST102TA_RightParacentral	ST43TA_LeftParacentral
ST104TA_RightParsOpercularis	ST45TA_LeftParsOpercularis
ST105TA_RightParsOrbitalis	ST46TA_LeftParsOrbitalis
ST106TA_RightParsTriangularis	ST47TA_LeftParsTriangularis
ST108TA_RightPostCentral	ST49TA_LeftPostCentral
ST110TA_RightPrecentral	ST50TA_LeftPosteriorCingulate
ST111TA_RightPrecuneus	ST51TA_LeftPrecentral
ST114TA_RightRostralMiddleFrontal	ST52TA_LeftPrecuneus
ST115TA_RightSuperiorFrontal	ST55TA_LeftRostralMiddleFrontal
ST116TA_RightSuperiorParietal	ST56TA_LeftSuperiorFrontal
ST117TA_RightSuperiorTemporal	ST57TA_LeftSuperiorParietal
ST118TA_RightSupramarginal	ST58TA_LeftSuperiorTemporal
ST119TA_RightTemporalPole	ST59TA_LeftSupramarginal
ST121TA_RightTransverseTemporal	ST60TA_LeftTemporalPole
ST129TA_LeftInsula	ST74TA_RightCaudalMiddleFrontal
ST130TA_RightInsula	ST82TA_RightCuneus
ST15TA_LeftCaudalMiddleFrontal	ST83TA_RightEntorhinal
ST26TA_LeftFusiform	ST85TA_RightFusiform
ST31TA_LeftInferiorParietal	ST90TA_RightInferiorParietal
ST32TA_LeftInferiorTemporal	ST91TA_RightInferiorTemporal
ST34TA_LeftIsthmusCingulate	ST94TA_RightLateralOccipital
ST35TA_LeftLateralOccipital	ST95TA_RightLateralOrbitofrontal
ST38TA_LeftLingual	ST99TA_RightMiddleTemporal
ST39TA_LeftMedialOrbitofrontal	ST40TA_LeftMiddleTemporal

3.2 Neuroimaging Only Analysis

3.2.1 Delusion Cohort

A total of 363 participants were identified from the ADNI database as meeting the inclusion criteria. Of these, n=143 endorsed symptoms of delusions (AD+D), and n=220 did not endorse symptoms of delusions (AD-D). Independent samples t-test comparing age, years of education, CDR global score, and MMSE total score identified a significant difference in MMSE total score between the two groups ($p < .001$), with the AD+D group on average having higher scores than the AD-D group. No significant differences were identified for any of the other covariates. Additional chi-square tests did not identify any group differences in sex distribution, MRI field strength, or number of ApoE4 alleles (Table 12).

A principal component analysis was conducted on the z-scores of 82 regions of interest with orthogonal rotation (varimax). The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis, KMO = .95. The rotation converged in 11 iterations and 13 components were identified that had eigenvalues over Kaiser's criterion of 1 and in combination explained 75.35% of the variance. The rotated component matrix was then used to identify ROIs that loaded most strongly to each component. No ROI loaded most strongly to component 12 and as such only components 1-11, 13 were retained for subsequent analyses. The 12 retained components reflected the following regions: 1) Bilateral frontal, parietal, occipital, and temporal, 2) bilateral orbitofrontal, middle frontal, frontal pole, orbitalis, 3) bilateral entorhinal cortex, amygdala, temporal pole, parahippocampal, insula, 4) left inferior, superior, middle, fusiform, isthmus cingulate, 5) bilateral caudal ACC, rostral ACC, posterior cingulate, right isthmus cingulate, 6) bilateral lingual, cuneus, pericalcarine, 7) right inferior temporal, superior temporal, middle temporal, fusiform, 8) bilateral pallidum, putamen, 9) bilateral caudate, 10) bilateral cerebellum, 11) bilateral thalamus, 13) bilateral accumbens area (Table 13). Component scores for each participant were also extracted for subsequent analyses.

The initial logistic regression analysis included the component scores for the 12 components described above in addition to the following covariates, age, sex, years of

education, CDR global score, MMSE total score, number of APOE4 alleles, and scanner strength. The overall model was significant $\chi 2(20) = 33.01$, $p = .034$. The model explained 11.8 % (Nagelkerke R^2) of the variance in delusions and correctly classified 66.9% of cases. The Wald criterion demonstrated that MMSE total scores (p= .004, Exp(B)=1.11 (95%CI: 1.04-1.20) made significant contributions to the presence of delusions. Trends towards significance were also identified for Component 2 (p= .068, Exp(B)=.80 (95%CI: .63-1.02), and Component 3 (p=.074, Exp(B)= 1.26 (95%CI: .98-1.62).

Table 12. Imaging only analysis: Delusion cohort demographic and disease profile

	Delusions (AD+D) N = 143		**No Delusions (AD-D) N = 220**			
	Mean	*(SD)*	Mean	(SD)	*t*	*p-value*
Age	74.80	*7.2*	75.94	*7.3*	1.5	.15
Years of Education	15.31	*3.0*	15.18	*2.8*	-0.41	.69
CDR Global Score	0.90	*0.46*	0.93	*0.42*	0.64	.52
MMSE Total Score	22.94	*4.3*	21.28	*4.2*	-3.66	<.001
	Males	*Females*	*Males*	*Females*	*Fischer's Exact Test (2-sided)*	
Sex (%)	52.4	47.6	58.6	41.4	0.279	
MRI Field Strength	*1.5T*	*3T*	*1.5T*	*3T*	*Fischer's Exact Test (2-sided)*	
	89	54	150	70	0.259	
	Delusions (AD+D)			**No Delusions (AD-D)**		
Number of ApoE4 alleles	*0*	*1*	*2*	*0*	*1*	*2*	*Pearson Chi-Square*
	42	72	29	75	100	45	.595

Table 13. Delusion Cohort: Rotated component matrix. Colours indicate ROIs loading most strongly to each component based on component scores. Loadings below 0.3 have been suppressed. R = Right, L=Left.

	Components												
FreeSurfer ROIs	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
R Precentral	0.85												
R Superior Parietal	0.83												
R PostCentral	0.825												
L Precentral	0.824												
L Post Central	0.807												
R Paracentral	0.803												
R Caudal Middle Frontal	0.799	0.322											
L Superior Parietal	0.795												
L Paracentral	0.791												
R Precuneus	0.79												
R Supramarginal	0.77						0.383						
L Precuneus	0.767			0.362									
L Caudal Middle Frontal	0.766	0.313		0.324									
R Inferior Parietal	0.757						0.413						
L Superior Frontal	0.717	0.481											
L Supramarginal	0.703			0.439									
L Inferior Parietal	0.688			0.521									
R Superior Frontal	0.677	0.555											
R Lateral Occipital	0.615					0.472	0.306						
R Pars Opercularis	0.606	0.451											
R Bank STS	0.601						0.482						
L Pars Opercularis	0.569	0.481											
R Pars Triangularis	0.552	0.542											
L Lateral Occipital	0.546			0.388		0.496							
L Transverse Temporal	0.48											0.431	
R Transverse Temporal	0.447	0.303										0.39	
R Lateral Orbitofrontal		0.746											
L Lateral Orbitofrontal		0.719		0.3									
L Pars Orbitalis		0.702											
R Frontal Pole		0.702											
L Frontal Pole		0.691											
R Pars Orbitalis		0.682											
R Rostral Middle Frontal	0.571	0.653											
R Medial Orbitofrontal		0.652			0.304								
L Medial Orbitofrontal		0.646			0.301								

L Rostral Middle Frontal	0.562	0.645										
L Pars Triangularis	0.472	0.552										
L Entorhinal			0.791									
R Entorhinal			0.761									
R Amygdala			0.704									
R Temporal Pole			0.692				0.336					
L Amygdala			0.689									
L Temporal Pole			0.648	0.305								0.351
L Parahippocampal			0.549		0.362							
R Parahippocampal			0.541		0.356							
R Insula		0.341	0.44		0.403		0.405					
L Inferior Temporal			0.32	0.712								
L Middle Temporal	0.474			0.672								
L Bank STS	0.524			0.589								
L Fusiform	0.384		0.342	0.581								
L Superior Temporal	0.452		0.384	0.488								
L Isthmus Cingulate	0.388			0.4	0.382							
L Caudal Anterior Cingulate					0.669							
L Rostral Anterior Cingulate		0.331			0.651							
R Caudal Anterior Cingulate					0.606							
L Posterior Cingulate	0.454				0.579							
R Posterior Cingulate	0.462				0.568							
R Rostral Anterior Cingulate		0.361			0.495							
R Isthmus Cingulate	0.323				0.495							-0.342
L Insula	0.305	0.308	0.395	0.306	0.402							
L Lingual	0.435			0.315		0.629						
R Cuneus	0.554					0.628						
R Lingual	0.458					0.615						
R Pericalcarine	0.512					0.611						
L Cuneus	0.517					0.597						
L Pericalcarine	0.518					0.566						
R Inferior Temporal	0.304		0.393				0.643					
R Middle Temporal	0.461		0.355				0.622					
R Superior Temporal	0.493		0.415				0.521					
R Fusiform	0.429		0.417				0.494					
L Pallidum								0.784				
R Pallidum								0.74				
R Putamen								0.636	0.509			
L Putamen								0.633	0.461			

L Caudate		0.877				
R Caudate		0.875				
R Cerebellum Cortex			0.903			
L Cerebellum Cortex			0.896			
R Thalamus				0.901		
L Thalamus				0.892		
L Accumbens Area						0.801
R Accumbens Area	0.419					0.581

3.2.1 Hallucination Cohort

A total of 233 participants were identified from the ADNI database as meeting the inclusion criteria. Of these, n=84 endorsed symptoms of hallucinations (AD+H), and n=149 did not endorse symptoms of hallucination (AD-H). Independent samples t-test comparing age, years of education, CDR global score, and MMSE total score did not identify any significant differences between the two groups. Additional chi-square tests did not identify any group differences in sex distribution, MRI field strength, or number of ApoE4 alleles (Table 14).

A principal component analysis was conducted on the z-scores of 82 regions of interest with orthogonal rotation (varimax). The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis, KMO = .94. The rotation converged in 12 iterations and 13 components were identified that had eigenvalues over Kaiser's criterion of 1 and in combination explained 76.63% of the variance. The rotated component matrix was then used to identify ROIs that loaded most strongly to each component. No ROI loaded most strongly to component 13 and as such only the first 12 components were retained for subsequent analyses. The 12 retained components reflected the following regions: 1) bilateral frontal, parietal and occipital regions, 2) bilateral orbital frontal, middle frontal regions, 3) bilateral entorhinal cortex, amygdala, temporal poles, parahippocampal, insula, 4) left middle temporal, inferior temporal, superior temporal, fusiform, isthmus cingulate, 5) right superior, inferior and middle temporal, 6) bilateral lingual and right pericalcarine, 7) bilateral caudal ACC, left ACC, left posterior cingulate, 8) bilateral pallidum, putamen, 9) bilateral caudate, 10) bilateral cerebellum, 11) bilateral thalamus, 12) bilateral accumbens area (Table 15). Component scores for each participant were also extracted for subsequent analyses.

The initial logistic regression analysis included the component scores for the 12 components described above in addition to the following covariates, age, sex, years of education, CDR global score, MMSE total score, number of APOE4 alleles, and scanner strength. The overall model was significant $\chi 2(20) = 43.39$ p = .002. The model explained 23.3 % (Nagelkerke R^2) of the variance in hallucinations and correctly classified 72.5% of cases. The Wald criterion demonstrated that Component 1 (p = .028, Exp(B) = 1.52

(95%CI: 1.05 - 2.20)), Component 2 (p=.012, Exp(B) = .644 (95%CI: 0.46 - 0.91)), Component 3 (p=.009, Exp(B) = 1.61 (95%CI: 1.13 – 2.29)), and Component 7 (p=.002, Exp(B)=.595 (95%CI: 0.43-0.83), made significant contributions to the presence of hallucinations. A follow-up logistic regression was conducted including only the variables that were identified as significant in the previous analysis. This included component scores for Components 1, 2, 3, 7. The overall model was significant $\chi 2(4) = 34.11$, $p < .001$. The model explained 18.7% (Nagelkerke R^2) of the variance in hallucinations and correctly classified 72.1% of cases. The Wald criterion demonstrated that Component 1 (p = .003, Exp(B) = 1.59 (95%CI: 1.18 - 2.12)), Component 2 (p=.024, Exp(B) = .699 (95%CI: 0.51 - 0.96)), and Component 3 (p=.001, Exp(B) = 1.67 (95%CI: 1.23 – 2.25)), Component 7 (p=.003, Exp(B)=.622 (95%CI: 0.46-0.85), made significant contributions to the presence of hallucinations..

Post-hoc analysis of covariance with FDR correction (q<.010) compared the mean cortical thickness and subcortical volumes for ROIs loading most strongly to Components 1, 2, 3, 7 between the AD+H and AD-H groups, with sex, age, years of education, CDR global score, and MMSE total score as covariates. Trends of larger cortical thickness were found for AD+H compared to AD-H in the following regions: left superior parietal (F(1,224)=4.31, p = .039, q = 0.307), left post central (F(1,224)=5.03, p =.026, q = .307), left cuneus (F(1,224)=4.1, p = .044, q = .307), left entorhinal (F(1,224)=6.5, p = .011, q = .055), right entorhinal (F(1,224)=6.9, p = .009, q = .055), left amygdala (F(1,224)=4.10, p = .044, q = .147). Trends for smaller cortical thickness for AD+H compared to AD-H were found in the following regions: left lateral orbitofrontal (F(1,224)=6.48, p = .012, q = .110), left medial orbitofrontal(F(1,224)=5.39 p = .021, q =. 110), right medial orbitofrontal (F(1,224)=4.7, p = .031, q = .116), and the right frontal pole (F(1,224)=5.32, p = .022, q = .110). Regions that were found to have significantly smaller cortical thickness values in AD+H subjects when compared to AD-H subjects included the left rostral anterior cingulate (F(1,224)=5.12, p = .025, q = .033), left caudal anterior cingulate (F(1,224)=10.25, p = .002, q = .004), and the right caudal anterior cingulate (F(1,224)=10.81, p = .001, q = .004).

Table 14. Imaging only analysis: Hallucination cohort demographic and disease profile

	Hallucinations (AD+H) N = 84		**No Hallucinations (AD-H) N = 149**				
	Mean	*(SD)*	Mean	*(SD)*	*t*	*p-value*	
Age	73.61	*7.3*	75.31	*6.7*	-1.8	0.07	
Years of Education	14.87	*3.0*	15.38	*2.7*	-1.3	0.19	
CDR Global Score	1.12	*0.57*	1.11	*0.32*	0.07	0.94	
MMSE Total Score	21.26	*5.3*	20.48	*4.3*	1.2	0.22	
	Males	*Females*	*Males*	*Females*	*Fischer's Exact Test (2-sided)*		
Sex (%)	52.4	47.6	54.4	45.6	0.786		
MRI Field Strength	*1.5T*	*3T*	*1.5T*	*3T*	*Fischer's Exact Test (2-sided)*		
	50	34	104	45	0.116		
	Hallucinations (AD+H)			**No Hallucinations (AD-H)**			
Number of ApoE4 alleles	*0*	*1*	*2*	*0*	*1*	*2*	*Pearson Chi-Square*
	22	45	17	47	69	33	.552

Table 15. Hallucination Cohort: Rotated component matrix. Colours indicate ROIs loading most strongly to each component based on component scores. Loadings below 0.3 have been suppressed. R = Right, L=Left

	Components											
FreeSurfer ROIs	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
R Superior Parietal	0.849											
L Superior Parietal	0.837											
R Precentral	0.825											
R Precuneus	0.824											
L Paracentral	0.818											
L Precentral	0.818											
R Paracentral	0.811											
L PostCentral	0.804											
R PostCentral	0.802											
L Precuneus	0.779			0.34								
R Caudal Middle Frontal	0.775	0.338										
L Caudal Middle Frontal	0.773	0.337		0.365								
R Inferior Parietal	0.772				0.405							
L Inferior Parietal	0.734			0.507								
R Supramarginal	0.728				0.43							
L Supramarginal	0.705	0.325		0.433								
L Superior Frontal	0.692	0.532										
R Superior Frontal	0.671	0.577										
R Cuneus	0.652					0.55						
R Lateral Occipital	0.642					0.433						
R Bank STS	0.607				0.529							
L Cuneus	0.598					0.513						
R Pars Opercularis	0.583	0.501										
L Lateral Occipital	0.563			0.375		0.498						
L Pericalcarine	0.557					0.516						
R Fusiform	0.502		0.417		0.387							
R Posterior Cingulate	0.495	0.321					0.46					
L Transverse Temporal	0.445	0.377										
R Isthmus Cingulate	0.388	0.382					0.333					
R Lateral Orbitofrontal		0.782										
L Pars Orbitalis		0.781										
L Lateral Orbitofrontal		0.745										
R Pars Orbitalis		0.688										

R Rostral Middle Frontal	0.499	0.687						
R Frontal Pole		0.687						
L Medial Orbitofrontal		0.686					0.315	
L Rostral Middle Frontal	0.523	0.664						
R Medial Orbitofrontal		0.653						
L Frontal Pole		0.64						
R Pars Triangularis	0.505	0.607						
L Pars Triangularis	0.468	0.599						
L Pars Opercularis	0.537	0.544		0.359				
R Rostral Anterior Cingulate		0.488					0.348	
R Transverse Temporal	0.414	0.419			0.362			
L Entorhinal			0.765					
R Entorhinal			0.756					
R Temporal Pole		0.377	0.7					
L Amygdala			0.698					
R Amygdala			0.678					
L Temporal Pole		0.387	0.611	0.31				
R Parahippocampal	0.332		0.499					
L Parahippocampal			0.492				0.36	
L Insula		0.415	0.422					
R Insula		0.409	0.471		0.472		0.309	
L Inferior Temporal				0.721				
L Middle Temporal	0.432	0.305		0.706				
L Fusiform	0.404		0.331	0.579				
L Bank STS	0.548			0.566				
L Superior Temporal	0.407	0.34	0.33	0.542				
L Isthmus Cingulate	0.378	0.308		0.495				
R Superior Temporal	0.492		0.375		0.582			
R Middle Temporal	0.515		0.329		0.577			
R Inferior Temporal	0.389	0.325	0.381		0.542			
L Lingual	0.455			0.341		0.636		
R Pericalcarine	0.53					0.591		
R Lingual	0.524					0.571		
L Rostral Anterior Cingulate		0.365					0.713	
L Caudal Anterior Cingulate							0.699	
R Caudal Anterior Cingulate							0.522	
L Posterior Cingulate	0.48			0.316			0.489	
R Pallidum								0.763
L Pallidum								0.76

R Putamen								0.608	0.451			
L Putamen								0.554	0.45			0.302
L Caudate									0.881			
R Caudate									0.871			
L Cerebellum Cortex										0.891		
R Cerebellum Cortex										0.888		
R Thalamus											0.854	
L Thalamus											0.853	
L Accumbens Area												0.712
R Accumbens Area			0.325									0.644

Chapter 4

4 Discussion

4.1 Discussion Overview

The biological mechanisms underlying psychotic symptoms in AD are poorly understood. Some patients with AD develop psychotic symptoms early in their disease course while others remain asymptomatic throughout. The discrepancy between participants that present with psychotic symptoms and those that do not provides an opportunity to investigate differences between these two groups of AD patients. In particular, it allows us to compare differences in neuroanatomical structures and genetic variants that could potentially mediate the presence of these symptoms in AD. As such, in our study we sought to investigate if the interactions between regional brain changes and genetic polymorphisms in neurotransmitter systems may be associated with the presence of delusions and hallucinations in AD.

Using PLS-CA we simultaneously assessed the interaction between 82 subcortical and cortical regions of interest and 15 SNPs in neurotransmitter systems to determine whether unique patterns of interactions may separate those with delusions, those with hallucinations, and those with both symptoms. Follow-up binary logistic regression analyses from a larger available sample were used to identify specific brain regions associated with the presence or absence of psychotic symptoms. For the delusion cohorts, results of the PLS-CA suggest that there are no significant interactions between neuroanatomical and genetic factors that distinguish those with delusions when compared to those without. In contrast, for the logistic regression analysis, although not significant we did identify a trend towards significance which suggests that cortical atrophy to orbitofrontal and middle frontal regions, coupled with relative preservation of temporal lobe structures may be associated with symptoms of delusions. The results for the PLS-CA for the hallucination cohort, suggest that individuals with AD and hallucinations may have a unique pattern of interactions in cortical regions and SNPs within the glutamatergic system when compared to those without hallucinations. Moreover, those with AD and symptoms of both delusions and hallucinations may have a distinct profile from those with just hallucinations even when matched for disease severity. Collectively, our findings suggest that delusions and hallucinations in AD may be associated with unique underlying neuroanatomic and genetic correlates and further highlight the

importance of investigating these as distinct symptoms of AD. These initial findings may also have implications for more specific and targeted treatment options for different psychotic symptoms in AD.

4.2 Delusions in Alzheimer's Disease

To investigate differences between AD patients that presented with symptoms of delusions, we conducted two main analyses - PLS-CA and a binary logistic regression analysis. Participants with available neuroimaging and GWAS data who presented with symptoms of delusions and a control group of AD patients that did not, were included in the PLS-CA. The binary logistic regression analysis included a significantly larger cohort of participants that had structural imaging data, and unlike the PLS-CA was not limited by GWAS availability. An important limitation to note for the PLS-CA, was that most, if not all participants only completed the NPI-Q. The abbreviated questionnaire does not distinguish between specific subtypes of delusions in AD. This is particularly relevant because the two main subgroups – paranoid and misidentification delusions, may have unique underlying correlates [154]. Moreover, delusions of theft, which are the most common subtype of delusions may be associated with memory impairments that arise as a result of AD. The lack of information with regards to specific subtypes of delusions that participants presented with may be a potential reason why we did not observe the hypothesized effects with regards to interactions between neuroanatomical and genetic factors.

In contrast, the binary logistic regression analysis identified a trend towards significance for Components 2 and 3. Component 2 included frontal lobe structures such as bilateral middle and lateral orbitofrontal, pars orbitalis, and frontal poles. Component 3 consisted predominantly of temporal lobe structures including bilateral entorhinal cortex, amygdala, parahippocampal, temporal poles, and the right insula. In particular, lower component scores for Component 2 and higher component scores for Component 3 were associated with an increased risk for delusions. These findings suggest that cortical atrophy of frontal lobe structures and relative preservation of temporal lobe regions may be necessary to generate symptoms of delusions in AD. This finding is consistent with the hypofrontality model of delusions which postulates that impaired frontal lobe function,

either arising from atrophy or hypometabolism, may be associated with the presence of delusions in AD [57,155,156]. In support of this model, a SPECT study of patients with AD and psychotic symptoms found that patients with delusions had hypoperfusion of the right frontal lobe when compared to those without delusions [66]. While another, through the use of voxel-based morphometry, found that patients with AD and delusions when compared to those without delusions had smaller grey matter volumes in bilateral parahippocampal gyrus, right posterior cingulate, right orbitofrontal cortex, bilateral inferior frontal cortex, right anterior cingulate, and left insula [157]. Although in our study we did not identify hemispheric lateralization with respect to delusional symptoms, the localization of these symptoms to the frontal lobe are consistent with prior studies. Furthermore, studies that directly assessed frontal lobe function through the use of cognitive rating scales found that psychotic symptoms in AD were associated with impaired working memory as measured by the digit span (forward and backward) task [158]. One other study looking specifically at frontal lobe function in patients with AD and delusions also found that patients with AD and delusional thoughts had lower overall scores on the Frontal Assessment Battery when compared to those without symptoms of delusions [159]. Based on the observed results, the authors hypothesized that impairments in executive functioning and not just episodic memory deficits may be associated with delusional thoughts. While the results of the binary logistic regression analysis showed a trend towards significance in frontal lobe regions, it may also be important to consider how other comorbid neuropsychiatric symptoms (i.e. depression, agitation, or apathy) may influence the presence of misidentification and paranoid delusions either through modulating attentional capacity or increasing susceptibility to paranoia.

4.3 Hallucinations in Alzheimer's Disease

Results of the PLS-CA identified a trend towards significance for Component 1. In particular, the interaction between smaller cortical thickness values in a number of frontal, temporal, and parietal regions and SNPs in the glutamatergic system distinguished those with hallucinations from those without. The glutamatergic system has previously been implicated in the NMDA receptor hypofunctioning hypothesis of schizophrenia which postulates that downregulation of glutamate signaling in prefrontal

regions which project to subcortical structural such as the amygdala, nucleus accumbens, and brainstem structures may lead to the development of positive symptoms [160–162]. More specifically, dysfunction in the cortical-brainstem circuitry arising from reduced glutamate signaling can lead to excessive dopamine release in the mesolimbic pathway, which can in turn result in hallucinations and delusions [163–165]. A previous study has similarly implicated a role of the GRIN2A receptor, in particular identifying an association between the homozygous recessive genotype of rs9922678 in the GRIN2A receptor and a bilateral reduction in hippocampal volume in patients with schizophrenia [166]. This finding is in line with the results of the PLS-CA which suggest that the homozygous recessive genotype of res9922678 may be associated with reduced cortical thickness in temporal lobe structures. This finding further supports our rationale that regional brain atrophy arising from AD may unmask the effects of SNPs in neurotransmitters systems. This is particularly relevant to approved medications that are used to treat neuropsychiatric symptoms in AD, given that antagonism of the NMDA receptor may actually contribute to the development of hallucinations in patients with AD. For instance, Memantine is a non-competitive NMDA antagonist that is often administered to patients with AD. This drug was designed to treat glutamate neurotoxicity which arises as a result of excessive activation of glutamate receptors, which in turn can lead to neuronal death. Although Memantine has been shown to have some benefits on cognition and overall function, one of the most frequent documented side-effects of this drug includes hallucinations in patients with AD [167–169]. Given, the risk of hallucinations that are associated with Memantine, not only is it important to address whether these symptoms in AD are a result of the drug, but also the effect of this drug on patients with existing genetic variants in NMDA receptors. Namely, whether the frequency and severity of hallucinations may be exacerbated in patients with genetic variants in NMDA receptors.

When considering the imaging data alone in the larger cohort, the logistic regression results were slightly different than the PLS-CA. In particular, the PLS-CA identified only regions that were smaller in those with hallucinations, while the binary logistic regression analyses identified regions with cortical thickness values that were larger and smaller in those with hallucinations when compared to those without. The main conflicting results

between the PLS-CA and binary logistic regression involved regions of the parietal lobe and the entorhinal cortex. Based on the PLS-CA these two regions were smaller in those with hallucinations when compared to controls, while in the binary logistic regression were larger in those with hallucinations, when compared to controls. The results of the binary logistic regression analysis suggest that larger cortical thickness in parietal, post-central, amygdala, cuneus, and entorhinal cortex regions and smaller cortical thickness in the anterior cingulate may be associated with symptoms of hallucinations. One possibility as to why these differences may exist may be consistent with our initial prediction. We posited that atrophy is necessary for unmasking the effects of SNPs, which may explain why the PLS-CA only identified ROIs that were atrophied in those with hallucinations when compared to those without. In contrast, the binary logistic regression analysis, which only looked at imaging variables in a larger sample, likely provides more information with regards to regions that are relatively preserved in those with hallucinations when compared to those without.

The findings from the logistic regression are in line with some previous studies in patients with AD which suggest that relative preservation of parietal, temporal, and occipital regions are necessary for the generation of hallucinations [87]. This particular pattern of frontal atrophy and preservation of temporal and posterior regions is also consistent with the case reports of Schneider and colleagues (1961), who noted that following localized lesions to the frontal lobe, patients who had suffered from previous falls or seizures developed hallucinations in the temporal and occipital lobes. The authors postulated that in this case abnormal activity was propagated along the uncinate fasiculus which connects frontal regions like the orbitofrontal cortex to temporal lobe and limbic structures [170]. More specifically, it is thought that lesions in frontal regions which through the uncinate fasiculus are connected to temporal lobe structures important for visual recall may lead to abnormal firing from the frontal lobe to these temporal lobe structures to generate symptoms of visual hallucinations. In future studies of psychosis in AD it would be of interest to evaluate if those with a frontal-variant of AD would be more susceptible to hallucinations, and to assess white matter connectivity, particularly tracts connecting the frontal lobes to the parietal and temporal regions.

The anterior cingulate itself also plays a key role in self-referential processing and discriminating between self-generated and external information and has been implicated in the generation of hallucinations in schizophrenia [171,172]. A SPECT study of psychotic symptoms in AD, also found that those with psychosis had lower regional perfusion in frontal regions such as the dorsolateral frontal, anterior cingulate, as well as other parietal and subcortical structures [173]. Given the role of the anterior cingulate, we suggest that atrophy of the anterior cingulate, which we identified in our study, may result in misattribution of external stimuli to internal states thereby resulting in symptoms of hallucinations. Importantly, the anterior cingulate also has extensive connections to limbic structures, including the amygdala and the insula, and has also been shown to be associated with the processing of negative emotions such as fear [174,175]. When tying this back to hallucination in AD, abnormal perceptions generated from inaccurate internal representation of stimuli may lead to an increased fear response, and distress in those experiencing hallucinations. This is particularly important given that this may be a contributing factor to the increased rates of institutionalization of patients with AD and hallucinations [82,83].

4.4 The Co-occurrence of Delusions and Hallucinations in Alzheimer's Disease

To investigate differences in patients with only delusions, only hallucinations, both hallucinations and delusions, and patients with neither symptom, we conducted a PLS-CA. The objective of this analysis was to try and identify differences that may exist on a neuroanatomical and genetic level, between individuals who present with particular or multiple symptoms of psychosis. Results of the PLS-CA identified a trend towards significance for Component 1. Namely, the latent factor plot and bootstrap confidence intervals suggest that those with hallucinations only (AD+H) and those with both delusions and hallucinations (AD+DH) may have a unique pattern of interactions between SNPs and ROIs. Although it is difficult to draw definitive conclusions given the small cohort sizes, multiple comorbid psychotic symptoms may be associated with more advanced cortical atrophy or simply a different pattern of cortical reorganization in response to the cognitive deficits that arise from AD. Given the results of our study which

suggest that patients with AD+DH have cortical thickness values below the grand mean in the large majority of ROIs when compared to those with just hallucinations, we speculate that disease severity may be driving the observed differences between the two groups. One study that looked into the frequency of neuropsychiatric symptoms and AD found an association between increasing frequency of delusions, hallucinations and aberrant motor activity with increased disease severity [176]. Although in our study the two groups did not differ in disease severity, it could be that those with AD+DH, while having more severe cortical atrophy, either have a different pattern of cortical reorganization or are able to use alternative compensatory cognitive strategies which may mask the degree of cognitive decline on clinical observation. Many studies that have described hallucinations in AD have tended to group together hallucinations and delusions into one overarching category of psychotic symptoms, which makes it difficult to parse underlying differences that may exist between the two. The findings of our study highlight the importance of investigating these symptoms as distinct phenomenon given the differences that we identified in the AD+H and AD+DH cohorts.

4.5 Limitations and Future Directions

This study was limited by the small sample size of participants endorsing symptoms of hallucinations and delusions. A replication cohort, potentially using individuals from the ADNI-2 database, may allow us to draw more definitive conclusions about the different interactions between brain regions and SNPs that may be associated with delusions and hallucinations. Furthermore, because many of the SNPs that we investigated were localized on the same chromosome, a haplotype analysis to detect SNPs that are in high linkage disequilibrium (more likely to be inherited together), may allow us to reduce the number of SNPs in our model and thereby increase the power of our study to detect associations between brain regions and genetic factors. In future studies, where we are powered to investigate more SNPs, it may be interesting to consider the interaction of neuroanatomical factors and SNPs in the serotonergic system. A previous study investigating the neuropathological and neurochemical correlates of psychosis in patients with AD, found that on post-mortem analysis, patients with psychotic symptoms had significantly reduced levels of serotonin in the prosubiculum and trends towards

reduction of serotonin in middle frontal, temporal, entorhinal cortex, and hippocampal regions [73]. Additional information with regards to SNPs in the serotonergic system that may be interacting with different brain regions may be of particular interest when considering the effects of newer antipsychotic treatments in patients with AD. For example, a newer drug by the name of Pimavanserin, a 5-HT2A inverse agonist, has been approved in the United States for the treatment of hallucinations in patients with Parkinson's disease. This drug is now also being tested for efficacy in patients with psychotic symptoms in AD. Early animal studies of this drug on psychotic symptoms in rodent models of AD, found that administration of Pimavanserin reduced psychosis-associated behaviours such as head twitches, excessive locomotor activity, and also normalized pre-pulse inhibition [177]. More recent human studies, including a randomized, double-blind, placebo controlled study investigating the efficacy of Pimavanserin in AD patients with hallucinations and/or delusions found that patients on the drug demonstrated significant improvements in psychotic symptoms when compared to those on placebo and did not experiences negative cognitive effects [178]. Given these findings, looking specifically at SNPs in the 5HT2A receptor and their interaction with SNPs in other neurotransmitter systems and brain regions, could provide us with more information on the specific mechanism by which hallucinations and delusions arise in patients with AD.

Furthermore, this study was limited because we were unable to dissociate between the specific subtypes of hallucinations and delusions within our cohorts. In future studies, where we are able to distinguish between the subgroups, it may provide us with more valuable information with regards to what particular subtypes of delusions or hallucinations may be driving the results that we obtained in our analysis. Given our findings of frontal lobe atrophy in patients with AD as well as frontal involvement in patients with hallucinations, in future studies it may be important to more specifically examine regions of hyper- and hypometabolism using fluorodeoxyglucose positron emission tomography (FDG-PET). This is because MRI data is limited in detecting only structural changes arising from regional cortical atrophy, which itself may not be easily identified in earlier stages of AD. FDG-PET may be a more powerful tool in detecting brain regions or networks that are abnormally hyper or hypo-active in response to disrupted cortical signaling. This in turn, may allow us to better understand the cortical

networks implicated in aberrant local and network-wide signaling which may give rise to symptoms of hallucinations and delusions in AD. Identifying networks of brain regions may then further guide diffusion tensor imaging studies to map white matter tracts that may be implicated in the pathology of psychotic symptoms in AD. This will allow us to better understand whether localized lesions to specific brain regions and/or connections between brain regions may be associated with AD+P.

5 Conclusions

In summary, the results of our study provide preliminary evidence of a unique signature of neuroimaging and genetic interactions which may be associated with the presence of hallucinations in AD. Specifically, these results suggest that genetic variants in the glutamatergic system, along with regional brain changes, may uniquely identify those with hallucinations. Although the results of the PLS-CA did not identify any significant differences in interactions between SNPs and ROIs, we did identify a trend towards significance in the logistic regression analysis which suggests that atrophy to the frontal lobe coupled with preservation of temporal lobe structures may be associated with symptoms of delusions in patients with AD. These findings further suggest that there may be distinct patterns of interactions that separate those with specific psychotic symptoms in AD from those without. Overall, knowledge of the interactions between SNPs in neurotransmitter systems and particular brain regions, may be an important starting point for earlier detection of those who may be susceptible to these symptoms in AD, and may allow for the development of more specific and targeted treatment options.

Appendix

Appendix A. Complete list of regions of interest included in analyses

List of 82 Regions of Interest	
ST110TA Right Precentral	ST130TA Right Insula
ST51TA Left Precentral	ST111TA Right Precuneus
ST74TA Right Caudal Middle Frontal	ST52TA Left Precuneus
ST15TA Left Caudal Middle Frontal	ST104TA Right Pars Opercularis
ST115TA Right Superior Frontal	ST62TA Left Transverse Temporal
ST56TA Left Superior Frontal	ST121TA Right Transverse Temporal
ST84TA Right Frontal Pole	ST72TA Right Bank Superior Temporal Sulcus
ST98TA Right Medial Orbitofrontal	ST36TA Left Lateral Orbitofrontal
ST114TA Right Rostral Middle Frontal	ST95TA Right Lateral Orbitofrontal
ST55TA Left Rostral Middle Frontal	ST46TA Left Pars Orbitalis
ST25TA Left Frontal Pole	ST105TA Right Pars Orbitalis
ST39TA Left Medial Orbitofrontal	ST106TA Right Pars Triangularis
ST116TA Right Superior Parietal	ST47TA Left Pars Triangularis
ST108TA Right Post Central	ST45TA Left Pars Opercularis
ST102TA Right Paracentral	ST13TA Left Bank Superior Temporal Sulcus
ST57TA Left Superior Parietal	ST34TA Left Isthmus Cingulate
ST49TA Left Post Central	ST24TA Left Entorhinal
ST43TA Left Paracentral	ST83TA Right Entorhinal
ST118TA Right Supramarginal	ST103TA Right Parahippocampal
ST90TA Right Inferior Parietal	ST44TA Left Parahippocampal
ST59TA Left Supramarginal	ST14TA Left Caudal Anterior Cingulate
ST31TA Left Inferior Parietal	ST73TA Right Caudal Anterior Cingulate
ST32TA Left Inferior Temporal	ST54TA Left Rostral Anterior Cingulate
ST40TA Left Middle Temporal	ST113TA Right Rostral Anterior Cingulate
ST26TA Left Fusiform	ST50TA Left Posterior Cingulate
ST58TA Left Superior Temporal	ST109TA Right Posterior Cingulate
ST119TA Right Temporal Pole	ST93TA Right Isthmus Cingulate
ST60TA Left Temporal Pole	ST53SV Left Putamen
ST117TA Right Superior Temporal	ST112SV Right Putamen
ST91TA Right Inferior Temporal	ST16SV Left Caudate
ST99TA Right Middle Temporal	ST75SV Right Caudate
ST85TA Right Fusiform	ST42SV Left Pallidum
ST82TA Right Cuneus	ST101SV Right Pallidum
ST23TA Left Cuneus	ST11SV Left Accumbens Area

ST107TA Right Pericalcarine	ST70SV Right Accumbens Area
ST48TA Left Pericalcarine	ST12SV Left Amygdala
ST97TA Right Lingual	ST71SV Right Amygdala
ST38TA Left Lingual	ST61SV Left Thalamus
ST35TA Left Lateral Occipital	ST120SV Right Thalamus
ST94TA Right Lateral Occipital	ST17SV Left Cerebellum Cortex
ST129TA Left Insula	ST76SV Right Cerebellum Cortex

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Conference Abstracts:

ORAL PRESENTATIONS

Ahmed, J., Robertson, A., Patel, S., Beaton, D., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2019). Regional brain structure interactions with genetic variants in neurotransmitter systems associated with hallucinations and delusions in Alzheimer's disease. American Neuropsychiatric Association 30th Annual Meeting, Chicago, Illinois.

Ahmed, J., Patel, S., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2018). Identifying biomarkers associated with the development of hallucinations and delusions in Alzheimer's disease: A multimodal neuroimaging and genetic analysis study. Clinical Neurological Sciences Research Day 2018, Western University.

POSTER PRESENTATIONS

Ahmed, J., Beaton, D., Robertson, A., Patel, S., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2019). Identifying neuroimaging and genetic correlates of delusions and hallucinations in Alzheimer's disease. Clinical Neurological Sciences Research Day 2019, Western University. **Best Poster Award.**

Ahmed, J., Robertson, A., Patel, S., Beaton, D., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2019). Interactions Between Brain Structures and Genetic Variants in Neurotransmitter Systems as Potential Biomarkers for Hallucinations and Delusions in Alzheimer's Disease. American Academy of Neurology 71st Annual Meeting, Philadelphia, Pennsylvania.

Ahmed, J., Beaton, D., Robertson, A.D., Patel, S., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2019). Identifying neuroimaging and genetic correlates of delusions and hallucinations in Alzheimer's disease. Parkwood Institute Research Day 2019, Parkwood Institute, London, Ontario.

Ahmed, J., Robertson, A., Patel, S., Beaton, D., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2019). Identifying neuroimaging and genetic correlates of delusions and hallucinations in Alzheimer's disease. London Health Research Day, Lawson Health Research Institute, London Health Convention Centre.

Ahmed, J., Robertson, A., Patel, S., Beaton, D., Palaniyappan, L., Pasternak, S., Masellis, M., Finger, E. (2019). Regional brain structure interactions with genetic variants in neurotransmitter systems associated with hallucinations and delusions in Alzheimer's disease. American Neuropsychiatric Association 30th Annual Meeting, Chicago, Illinois.

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