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Does the APOE ε4 Allele Moderate a CA1 Atrophy and Psychotic Symptomatology Relationship in Alzheimer's Disease?

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by

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ABSTRACT

There are an estimated 6.1 million Americans currently diagnosed with Alzheimer's disease (AD) with this number expected to rapidly grow over the next 30 years. Delusions are reported in roughly one-third of individuals with AD (Ropacki & Jeste, 2005). Delusions in AD are related to worse outcomes; greater caregiver burden, functional decline, and overall, worse general health (Murray et al., 2014). Current treatment options are limited given the health risks related to antipsychotics in the elderly (Creese et al., 2018). In the current study, we examined the relationship between APOE ε4 allele status, CA1 subfield volumes, and the presence of delusions in a combined Alzheimer's disease dataset (OASIS and ADNI) in a two-prong fashion. First, we examined the moderating effect of APOE ε4 allele on the relationship of the CA1 volumes and delusions and MMSE scores, separately. Second, we examined the specificity of that effect by comparing CA1 volumes to other hippocampal subfields in a repeated measure model. Individuals with delusions had smaller right CA1 volumes than individuals without delusions but this was unrelated to APOE ε4 alleles. There was no significant moderation of the APOE ε4 alleles on the relationship between the CA1 subfields and the presence of delusions. There was a significant relationship between left CA1 volumes, APOE ε4 allele presence, and MMSE scores. These findings do not completely dissuade a subcortical relationship with delusions as no other notable differences between individuals with delusions and individuals without delusions were found in demographic information, genetic information, or cognitive measures. Future research is needed to examine the relationship between the hippocampus and delusions in other imaging capacities (e.g., longitudinal studies, functional connectivity) and along more detailed presentations of delusions.

INDEX WORDS: Alzheimer's disease, APOE, Hippocampus, CA1, Delusions, Psychosis

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DEDICATION

This dissertation is dedicated to my parents.

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INTRODUCTION AND LITERATURE REVIEW

1.1 Purpose of the Study

Alzheimer's disease (AD) is the fifth leading cause of death in individuals over 65 years old and affects roughly 6.1 million Americans (Kochanek et al., 2020; Matthews et al., 2019). AD is a progressive disease characterized by increasing cognitive impairment with comorbid presentations of motor deficits, depression, irritability, hallucinations, and delusions (Murray et al., 2014). Psychosis in Alzheimer's disease (AD) is estimated between 10 and 73% with an average prevalence of approximately 50% (Fischer & Sweet, 2016; Murray et al., 2014; Tzeng et al., 2018). Delusions are reported in roughly one-third of individuals with AD (Ropacki & Jeste, 2005) and in roughly half of individuals with dementia with Lewy bodies (DLB) (Tzeng et al., 2018). Delusions in AD are related to worse outcomes: greater caregiver burden, higher rates of institutionalization, functional decline, and overall, worse general health (Murray et al., 2014). Current treatment options typically involve antipsychotics; however, antipsychotics are known to increase risk for falls, cardiovascular issues, blood clots, stroke, and overall sedation in elderly individuals, and therefore need to be administered with caution. Understanding the genetic and neural underpinnings of delusions in AD can help inform what genetic factors are interacting with neurodegeneration that relate to a vulnerability to the development of delusions and therefore, point towards new treatment options such as transcranial magnetic stimulation (TMS) that can target (directly and indirectly) nerve cells in specific regions to moderate symptoms associated with dysfunction in those regions.

One of the strongest genetic risk factors for AD is the apolipoprotein E (APOE) (ε4) allele. The APOE ε4 allele accounts for approximately 50-60% of the genetic variation in AD (Cacabelos

et al., 2003; Liu et al., 2013; Stocker et al., 2018). Possession of one APOE ε4 increases risk between 2- and 4-fold for developing AD, whereas possession of two APOE ε4 alleles increases risk 8- to 12-fold (Belloy et al., 2019; Liu et al., 2013). Although APOE ε4 is a known major genetic risk factor for AD, mere possession is not sufficient or direct enough to cause AD. The exact mechanisms involved in this pathogenesis and how it relates to AD are still not fully understood. In addition to its known risk for AD, the APOE ε4 allele has been associated with other clinical phenotypes, more severe positive symptoms (hallucinations and delusions) in people with schizophrenia, and the psychosis phenotypes of AD (Burke et al., 2016; Christie et al., 2012; Digney et al., 2005; Zubenko et al., 1996). The APOE ε4 allele appears to relate to, or at least influence, multiple phenotypes of psychiatric or neurogenerative presentations. However, how the APOE ε4 allele relates to specific phenotype of AD and delusions is still not fully understood. Therefore, examination of the overlap of gray matter atrophy in the hippocampus found in AD (Möller et al., 2013; Padurariu et al., 2012) and psychosis (specifically delusions) (Guimond et al., 2021), and the APOE ε4 genotype (Taylor et al., 2014a) is an important next step in understanding the potential association between this genotype and the unique clinical phenotype of delusions in AD.

The CA1 subfield of the hippocampus has been implicated in novelty detection, autobiographical memories, and autonoetic consciousness (Bartsch et al., 2011a). The CA1 subsfield has previously been implicated in individuals presenting with psychosis, not specific to any one disorder. Pyramidal cell death in the CA1 was originally hypothesized as the cause of paranoid delusions (Krieckhaus et al., 1992). In addition, shape deformity of the CA1 has been correlated with delusion and hallucination severity in schizophrenia (Zierhut et al., 2013). In AD,

carriers of the APOE ε4 allele exhibit greater hippocampal volume loss, specifically in the CA1 region (Kerchner et al., 2014; Padurariu et al., 2012).

The overlap in gray matter alterations identified in the hippocampus, specifically in the CA1 region, in AD, delusions, and APOE ε4 status indicate potential support for an association between the APOE ε4 allele and delusions. The question remains if CA1 atrophy is associated specifically with delusions in AD, and if so, how does the presence of the APOE ε4 allele relate to the shape deformity and/or volumetric changes in the CA1 subfield. Further research is needed to identify if the relationship between APOE ε4 allele, CA1 atrophy, and delusions is specific to AD, all disorders that present with delusions, or merely correlational to the presence of AD. The aims of this study are to examine the association of delusions with CA1 volumes and the presence of APOE ε4 alleles within an AD population.

1.2 Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common type of dementia; a progressive, neurodegenerative disease that is associated with impaired memory and cognitive decline (American Psychiatric Association, 2013). Other types of dementias include Lewy Body dementia (LBD), vascular dementia, and frontotemporal dementia, each of which make up roughly 5-10% of individuals diagnosed with dementia. In addition to its progressive neurocognitive impairment, AD is categorized by the presence of beta-amyloid plagues and tau neurofibrillary tangles within the brain (Ballatore et al., 2007; Dickson & Vickers, 2001; Masters & Selkoe, 2012). AD can also present with motor deficits, and neuropsychiatric symptoms such as depression, irritability, and psychosis (hallucinations and delusions). It is estimated that psychosis prevalence in AD is roughly 50% of cases with delusions being present is roughly one-third of all AD patients (Fischer & Sweet, 2016; Murray et al., 2014; Ropacki & Jeste, 2005). The presentation of psychosis in AD

can be difficult to diagnose partially because individuals with AD may be completely free of psychosis for years prior to the first noted presentation (Fischer & Sweet, 2016b; White & Cummings, 1996). Psychosis presentation in AD is more common in the middle to later stages of the disease and therefore, may be presenting alongside more severe neurocognitive symptoms (Murray et al., 2014; Sweet et al., 2003b). In addition, psychosis in AD is often associated with adverse outcomes including aggression, agitation, functional impairment, behavioral symptoms, rapid cognitive decline, mortality, and increased caregiver burden (Murray et al., 2014). Within dementia, delusions have been associated with distinct neurobiological mechanisms including abnormalities on fronto-dementia (FTD) genes (C9orf72, MAPT, GRM) and more severe disease severity (Kumfor et al., 2022). Therefore, examining the specific neural and genetic underpinnings of delusions in AD may help in understanding the mechanisms behind this severe sub-presentation of dementia.

1.3 Apolipoprotein (APOE) ε allele

The APOE gene is polymorphic and has three different variants: APOE ε2, APOE ε3, and APOE ε4, see Table 1 for more details. Two specific single nucleotide polymorphisms (SNPs) found within the APOE gene, *rs*429358 and *rs*7412, of chromosome 19q13.32 with the three different variants all having different methylation levels. Every individual has two copies of the APOE gene, leading to six possible combinations. The function of the APOE gene is largely lipid transport and cholesterol homeostasis. Dysregulation of these functions, lipid metabolism and homeostasis, has been ascertained as a contributor of degenerative disorders (Bleasel et al., 2014; Sultana et al., 2013). In addition to lipid transport, the APOE gene has been implicated in increased inflammation responses (less injury repair), decrease in synaptic signaling, mitochondrial function, and degradation of the blood brain barrier integrity. The current theory is that specific APOE

genotypes relate to adverse or slowed reactions to injury. For example, normal aging can be thought of as a cumulation of tiny injuries or degeneration and therefore, APOE ε4 allele is related to less repair as the brain ages (Reinvang et al., 2013; Washington & Burns, 2016). Individuals with the APOE ε4 allele also have higher levels of plasma and neuronal cholesterol (de Chaves et al., 2008; Jeong et al., 2019). Specific to APOE ε4 allele, individuals with at least one copy of this variant have an increased risk of developing Alzheimer's disease (AD) and coronary artery disease (CAD) (Mahley, 2016; Stocker et al., 2018).

Table 1. APOE variants.

	SNP alleles	
APOE variant	*rs*429358	*rs*7412
ε4	C	C
ε3	T	C
ε2	T	T

APOE Genotype	*rs*429358	*rs*7412
ε4ε4	CC	CC
ε3ε4	TC	CC
ε2ε4	TC	TC
ε3ε3	TT	CC
ε2ε3	TT	TC
ε2ε2	TT	TT

The APOE ε4 allele accounts for approximately 50-60% of the genetic variation in AD (Liu et al., 2013). Possession of a single copy of the APOE ε4 allele is related to a three-fold risk of developing AD, while the ε4/ε4 genotype is associated with a 14-fold increase in disease risk (Belloy et al., 2019; Corder et al., 1993). The APOE ε4 allele is also associated with a decreased age of AD onset and decreased survival (Belloy et al., 2019; Corder et al., 1993). The association between APOE ε4 and AD is thought to be related to the increase in amyloid beta aggregation and toxicity and reduction of amyloid beta clearance, all of which lead to a buildup of amyloid plagues,

the common presentation of AD. The APOE ε4 allele is associated with an earlier presentation of amyloid, further supporting its role in early-onset AD (Kanekiyo et al., 2014; Tachibana et al., 2019). Individuals with one or two ε4 alleles have the most amyloid beta and those with the APOE ε2 allele(s) have the least amount of amyloid beta (Kanekiyo et al., 2014). Therefore, the APOE ε2 allele is assumed to be a protective factor against AD and even other disorders (e.g., mood disorders).

APOE and the brain

APOE is reported in high levels in the temporal lobe, putamen, hippocampus, caudate, precentral gyrus, and cerebellum and these regions may aid in determining the mechanisms in which APOE ε4 relates to brain dysfunction (Digney et al., 2005b; Flowers & Rebeck, 2020; Holtzman et al., 2012). Structural MRI studies have found an association between the APOE ε4 allele and hippocampal volume loss in both smaller baseline volume and higher rate of gray matter loss in AD (Cacciaglia et al., 2018; Schuff et al., 2008; Taylor et al., 2014b). In a longitudinal study, homozygous APOE ε4 carriers had significant unilateral atrophy in the head of the right hippocampus compared to heterozygous APOE ε4 carriers (Li et al., 2016). More specifically, carriers of the APOE ε4 allele exhibit greater hippocampal volume loss, specifically in the Cornu ammonis (CA1) subsection of the hippocampus, known for novelty detection and autonoetic consciousness (Bartsch et al., 2011; Kerchner et al., 2014; Padurariu et al., 2012). Less gray matter concentration was also identified in carriers of the APOE ε4 allele(s) in both the posterior cingulate and amygdala (Haller et al., 2017).

Regarding diagnoses, the APOE ε4 allele has also been implicated in a variety of disorders and symptom phenotypes; individuals with schizophrenia, psychosis phenotypes of AD, mood disorders, and Lewy body dementia (Burke et al., 2016; Digney et al., 2005; Jonas et al., 2019;

Zubenko et al., 1996). An increased odds ratio of 3.11 [95% CI 1.21-8.01] between the APOE ε4 allele and delusions was identified in individuals with Alzheimer's disease (Spalletta et al., 2006). However, this association has not been consistently found in more recent research (del Prete et al., 2009; Qian et al., 2018). APOE ε4 also appears to play a role in cognition, specifically attention and memory. In individuals with Parkinson's disease, APOE ε4 is also related to faster (and overall) cognitive decline but an increased risk of dementia was not consistently identified (Kurz et al., 2009; Mata et al., 2014; Paul et al., 2016). In middle-aged adults without dementia, the APOE ε4 allele was related to impairments in the ability to shift attention from irrelevant stimuli and in spatial working memory tasks (Greenwood et al., 2005). These findings suggest that the APOE ε4 allele may moderate selective attention and spatial working memory even in cognitively typical adults.

As mentioned previously, APOE ε4 allele possession is related to a higher risk of AD, but in addition the APOE ε4 allele is related to worse overall AD symptoms, increased inflammation responses, decrease in synaptic signaling, and lower injury recovery (Flowers & Rebeck, 2020). It has also been hypothesized that APOE ε4 allele is related to slower brain development as presence of the allele was negatively related to temporal lobe gray matter in neonates (Taylor et al., 2014a). A reduction in gray matter may indicate lower tissue reserve, which may be part of the association with AD but could also explain the association between the APOE ε4 allele and brain disorders in general. We hypothesize that, given its negative implications especially in neural injury recovery, the ε4 allele may also moderate the associations of gray matter atrophy (specifically in the hippocampus) and neuropsychiatric symptoms observed in AD.

CA1 Subfield of the Hippocampus

The subfields of the hippocampus have unique cytoarchitecture and each subfield is thought to play distinct roles with different cognitive processes. The hippocampal subfields include the cornu ammonis (CA1, CA2, and CA3), dentate gyrus, the presubiculum, and the subiculum. See Figure 1 originally printed in (Travis et al., 2014).

Figure 1. Segmentation of the Hippocampal subfields from Travis et al., 2014.

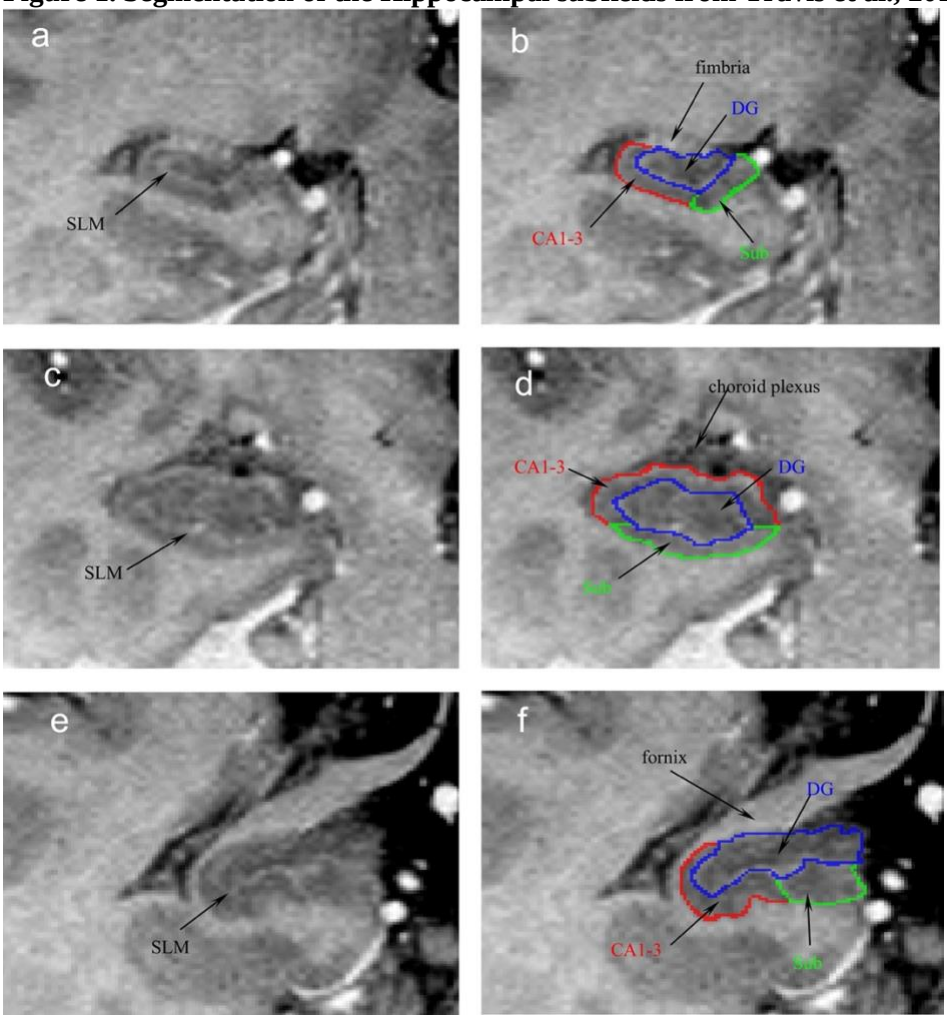


Fig. 1. Figure originally printed in Travis et al., 2014. Segmentation of the hippocampus (HC) subfields within HC sub-regions is shown on T2-weighted Fast Spin Echo (FSE) images using inverted contrast: coronal views of the hippocampal body (a and b); hippocampal head (c and d); hippocampal tail (e and f). Abbreviations: CA1–3=cornu ammonis (shown in red); DG=dentate gyrus (shown in blue); sub=subiculum (shown in green); SLM=stratum lacunosum-moleculare

Spanning both the anterior (head) and posterior (tail) hippocampal regions, the Cornu ammonis (CA1) has been implicated in novelty detection, information input comparison, and autobiographical memory. More specifically, the CA1 region has most notably been studied in autonoetic consciousness, the ability to reflect on one's own life and experiences and perceive continuity from past, present, and future events (Bartsch et al., 2011a). Given its hippocampal placement and its role in autobiographical memory, CA1 shape deformity has been consistently implicated in AD and other dementias (Padurariu et al., 2012). The CA1 has also been implicated in individuals with schizophrenia (Schobel et al., 2009; Zierhut et al., 2013).

Pyramidal cell death in the CA1 was previously hypothesized as a primary cause of paranoid delusions (Krieckhaus et al., 1992). In schizophrenia, CA1 volume reduction and shape deformity have been negatively associated with overall delusion severity and hallucination severity (Zierhut et al., 2013). Lower neuron counts in the CA1 were related to misidentification delusions (Förstl et al., 1994) and focal brain lesions were identified in the CA1 regions of individuals who presented with Capgras delusion (Feinberg & Keenan, 2005). It had previously been reported that CA1 connectivity was related to overall positive symptoms (Schobel et al., 2009). Theoretically, hyperactivation of the CA1 may relate to a disturbed processing of information, and that may be predictive of positive symptoms. It is possible that this subregion is broadly related to psychosis and not specifically, delusions. The atrophy observed in the CA1 may be caused by hyperactive hippocampal states that ultimately result in neuronal or glial loss throughout the course of the disease. If this is the order of operations, then this atrophy could be identified in a host of disorders the relate to hyperactivity in the hippocampus, not just AD. There is some evidence for association between the dopamine-related gating at CA1 and delusions of misidentification, a common delusion type observed in AD (Ismail et al., 2012).

1.4 Delusions

Delusions are categorized as fixed, false beliefs that are maintained despite contrary evidence (American Psychiatric Association, 2013). Referred to as a form of psychosis, delusions are a hallmark of schizophrenia and one of the main diagnostic criteria for the disorder (American Psychiatric Association, 2013; Maher, 2006). Delusions also present transdiagnostically, in neurodegenerative diseases, nervous system disorders, stroke patients, traumatic brain injuries, and other psychiatric disorders. There is even, albeit rare (current prevalence rate of 0.2%), a standalone diagnosis of delusional disorder that can remit naturally, maintain with reduced intensity, or result in a change of diagnosis to schizophrenia (American Psychiatric Association, 2013; Opjordsmoen, 2014). Delusions, regardless of primary disorder, are associated with increased caregiver burden, poorer medication adherence, and overall, worsening prognosis across disorders and can severely impact functioning and independent living (Altamura et al., 2018; Fischer & Sweet, 2016; Ismail et al., 2011; Warren et al., 2018; Whitehead et al., 2012).

Delusion type falls broadly into twelve different categories with some discrepancies: persecutory, jealousy, grandiosity, religious, delusion of reference, erotomania, guilt, somatic, and passive delusions such as, thought withdrawal, thought insertion, thought broadcasting, and the delusion of being controlled. There are additional categories of delusions that are more specific and common in Alzheimer's disease, such as Capgras delusion (believing family members are replaced by an identical imposter) and Othello's syndrome (delusional jealousy about family members) (Moro et al., 2013). Different types of delusions may be associated with co-occurring symptoms (e.g., mood states) and overall clinical presentations that are etiologically heterogeneous. In AD, the most common types of delusions are persecutory (or paranoia) and delusions of misidentification (e.g., Capgras delusion). Furthermore, different types of delusions

may indicate different underlying psychopathological constructs (e.g., deficits in self-monitoring versus deficits in source monitoring (Blakemore et al., 2000; Corlett et al., 2010).

Current Hypotheses on the Development of Delusions

Delusions: The Dopamine Dysfunction Hypothesis. The salience network involving the bilateral anterior insula and anterior cingulate cortex has been implicated in error monitoring and processing of salience pathway. In functional studies, the anterior insula cortex and the anterior cingulate cortex are activated during errors in performance and error awareness (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012; Klein et al., 2007; Ullsperger et al., 2010). Specifically, the insula-cortico-thalamic circuit, including the dorsal and ventral areas of the anterior insula, is responsible for both error awareness and the processing of salience (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012). Psychosis has been shown to be associated with a dysfunction of the dopamine-dependent process of salience attribution (Kapur, 2003; Maia & Frank, 2017). Specifically, an increase in striatal dopamine synthesis capacity is related to psychosis progression (Howes et al., 2011). In schizophrenia, however, the disruption may be further explained by a combination of increased dopaminergic activity for irrelevant stimuli and a decrease in dopaminergic activity regarding situation relevant stimuli (Maia & Frank, 2017). The mechanism of antipsychotic medications, mostly through dopamine (D2) antagonism (B. Li et al., 2016), suggests a causal relationship between psychosis and dopaminergic disruptions. However, it should be noted that this dopamine dysregulation model has mostly be developed in the context of psychosis in schizophrenia. Similarly in Alzheimer's disease, an excess of striatal dopamine D2/3 receptors was found to be related to delusion presence (Reeves et al., 2012). Levodopa (L-dopa), a precursor to dopamine, is the gold-standard medication for Parkinson's disease, though may result in the formation of delusions and hallucinations (Ruggieri et al., 1997; Swick & Walling, 2005). A recent study found

that 81% of Parkinson's disease patients developed psychosis after being on a dopamine replacement therapy (e.g., levodopa) (Dave et al., 2020). However, this association is not specific to delusions, such that there are remaining questions as to specificity of the relationship between dopamine dysregulation and delusions.

The mesolimbic pathway is a collection of dopaminergic neurons beginning at the ventral tegmental area in the midbrain and connecting to the ventral striatum (including the nucleus accumbens) of the basal ganglia in the forebrain. The release of dopamine into the nucleus accumbens regulates motivational salience, influences drive and behavior, and reward-based learning whereas release of dopamine in the dorsomedial prefrontal cortex is more related to effort learning (e.g., cost and benefits) (Chong, 2018; Kapur, 2003). The current understanding is that disruptions in the dopaminergic system may result in misread salient information, attention to irrelevant stimuli, and ultimately, disruptions to reward-related behavior (Howes & Nour, 2016; Kapur, 2003; Winton-Brown et al., 2014). Individuals with schizophrenia and psychosis have been shown to assign overt salience to contextually irrelevant stimuli, potentially because of this disruption of dopamine release (Kapur et al., 2005; Katthagen et al., 2022; Menon et al., 2022). This disruption may explain (at least initially) the divergence of belief formation and belief updating into psychosis formation. Therefore, this framework may begin to explain not only formation of delusions but hallucinations as well.

Delusions: Deficits in Error Monitoring. Delusions have previously been conceptualized as the result of defects in error monitoring, perhaps related to a disruption in dopaminergic pathways (Corlett et al., 2010; Krummenacher et al., 2010). Deficits in the ability to differentiate information-bearing patterns from noise result in noise taken in as salient information, also referred to as deficits in signal detection. Corlett and colleagues described this deficit as a two-factor model

(Corlett et al., 2010). First, the predictor error, or a discrepancy between the brain's prediction of a stimulus and the actual perception of that stimulus, occurs, and second, abnormal stimulus information is integrated into previous knowledge (Corlett et al., 2010). More specifically, the discrepancy between prediction and stimulus perception results in incorrect attention towards potential explanatory cues and subsequently, learning of misrepresentations of the environment, resulting in the formation of a delusion (Corlett et al., 2010; Corlett & Fletcher, 2015). Individuals with schizophrenia have been shown to have impaired error monitoring and importantly, defects in error awareness (Mathalon et al., 2002). Prediction errors, in a deficit model for psychosis, have been associated with the dorsolateral prefrontal cortex and the right middle/frontal gyrus (Griffiths et al., 2014). Previous structural studies have also implicated the left inferior frontal gyrus (IFG) in error monitoring (Mitchell et al., 2009; Sharot & Garrett, 2016). As previously mentioned, the dopaminergic system also plays a role in signaling errors related to reward (or salience) prediction (Schultz & Dickinson, 2000). In functional studies, the anterior insula cortex and the anterior cingulate cortex are activated during errors in performance and error awareness (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012; Klein et al., 2007; Ullsperger et al., 2010). Specifically, the insula-cortico-thalamic circuit, including the dorsal and ventral areas of the anterior insula, is responsible for both error awareness and the processing of salience (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012). Given the study populations, it is unclear if this theory explains all delusion formation or relates only to delusions in patients with schizophrenia.

Delusions: Cognitive Biases. Additional theories have been postulated about delusions being a form of cognitive bias. This theory states that the maintenance of delusional thinking requires a two-sided approach, or bias, to incoming information. There is a predilection for information supporting the delusion (confirmatory evidence), and an avoidance (or rejection) of

evidence not supporting the delusion (non-confirmatory evidence) (Moritz & Woodward, 2006; Woodward et al., 2006). Specifically, cognitive biases such as jumping to conclusions, biases against disconfirming evidence (BADE), and liberal acceptance are more commonly seen in individuals with schizophrenia and delusions than healthy populations without psychosis (Moritz & Woodward, 2006; Veckenstedt et al., 2011).

Functional studies found the jumping-to-conclusion bias was associated with the dopaminergic reward system and the posterior cingulate cortex (Andreou et al., 2018). Bias against disconfirming evidence (BADE) was associated with increased visual network activity and reduced default mode network (DMN) activity when processing confirmatory evidence, and reduced activation in the orbitofrontal cortex, inferior frontal gyrus, and parietal cortex when processing disconfirming evidence in individuals with schizophrenia with delusional ideation (Lavigne et al., 2020).

These cognitive bias theories have all been suggested as separate explanations for the etiology of delusions. These theories may help to explain why delusions feel “real” to the individual and do not elicit scrutiny or questioning even in the face of contrary evidence. Together, the deficits in error monitoring and cognitive biases theories present the two main stages of delusions: formation and maintenance. In other words, the delusion begins with an error in the processing of stimuli (a default) followed by avoiding the contradictory evidence while seeking out confirming evidence (a bias) to maintain the delusion. However, the theories have largely only been examined with individuals with schizophrenia or healthy volunteers using cognitive-based tasks (e.g., oddball task, antisaccade task) that represent circuits that underlie delusions. It remains unclear if these tasks activate the same the networks involved in delusion formation and maintenance. In addition, as most studies examining the neurobiology and neuroanatomy of

delusions focus on schizophrenia, it remains unclear if these theories of etiology and related circuitries generalize across the different diagnoses where delusions are present, such as AD. Although delusions can occur in a multitude of disorders, there may be unique etiology to delusions in AD given that psychosis presentation in AD typically occurs in the middle to later stages of the disease (Sweet et al., 2003a). The delayed onset of delusions (as opposed to at first diagnosis) may indirectly relate to the course of AD and the degradation of cortical structures.

1.5 Delusions: Gray Matter Alterations

Across diagnoses, structural studies identified that delusions were related to varying degrees of alteration in the frontal and temporal regions (Rootes-Murdy et al., 2022). Although, there were some inconsistencies in the directionality of the gray matter alterations (Zhu et al., 2016), delusions were most associated with gray matter reductions in the dorsolateral prefrontal cortex (in individuals with SZ, bipolar disorder (BP), and AD), left claustrum (SZ and AD), insula (SZ, BP, and AD), thalamus (SZ and AD), superior temporal gyrus (SZ, BP, and AD), and middle frontal gyrus (SZ, BP, AD, and Parkinson's disease), and the hippocampus (SZ and AD). The individual functions associated with these regions may explain the relationship with delusions.

The claustrum is related to cognitive control, multi-sensory integration, consciousness, and task switching as well as cortically connected to the insula and the default mode network (Krimmel et al., 2019). The insula relates to proprioception and the sense of self, self-awareness, more specifically, the posterior part of the insula is related to attention to and processing of salience (Craig, 2002; Harsay, Spaan, Wijnen, & Ridderinkhof, 2012). The hippocampus is primarily responsible for both short-term and long-term memory storage and retrieval (Squire, 1992) as well as declarative memory, recollection of recognition memory, episodic memory, and familiarity (Bird, 2017; Brown & Aggleton, 2001; Kim, 2015) and along with the amygdala, salient

information processing (Zheng et al., 2017). The posterior region of the superior temporal gyrus (specifically Wernicke's speech area, BA 22) is associated with auditory processing (Howard et al., 2000), and the caudal region relates to sentence comprehension (Hamilton et al., 2018). The thalamus serves as a relay station between internal and external information as well as being structurally related to the hippocampus, limbic system, and fornix. Specifically, the thalamo-cortical neurons are responsible for receiving external sensory information and relaying it upstream (Torrico & Munakomi, 2019) whereas the cortico-thalamo-cortical loop has been implicated in the maintenance of consciousness and attention to incoming visual stimuli (Trapp et al., 2012).

However, it should be noted that these identified regions are also typically implicated in psychiatric disorders, neurodegenerative disorders, and nervous system disorders like Parkinson's disease and may be related to either the neural deterioration commonly seen in psychiatric disorders (DelBello et al., 2004; Gupta et al., 2015; Kempton, 2011; Lorenzetti et al., 2009; Torres et al., 2016), or the genetic and neural overlap amongst schizophrenia and bipolar disorder with psychosis (Tamminga et al., 2017), and less related to delusions specifically. Therefore, these regions can be viewed as a starting point for examining the cortical alterations associated with delusions but are not fully explaining the etiology of delusions.

1.6 Delusions in Alzheimer's Disease: Gray Matter Alterations

One cortical region that has consistently been altered in AD is the hippocampus, known for its role in short and long-term memory, memory encoding, social interactions, and flexible cognition (Li & Liu, 2019; Möller et al., 2013). Importantly, the hippocampus is thought to be one of the first brain regions that is affected in AD. However, by the time most patients are diagnosed with AD, multiple brain regions can be and typically are altered, whether it be from the disease or

natural aging, making it difficult to differentiate primary from secondary sites of dysfunction. These areas are also differentially vulnerable to disease (and aging) mechanisms. As previously mentioned, structural MRI studies have found that delusions in AD are correlated with less gray matter in the right frontoparietal, left frontal lobe, right hippocampus, and the left claustrum (Bruen et al., 2008; Serra et al., 2010a). Specific to women with Alzheimer's disease and paranoid delusions, there was noted atrophy in the left lateral and medial orbitofrontal and superior temporal regions (Whitehead et al., 2012). In addition, there was also less gray matter in the sensorimotor area (Brodmann's Area (BA) 6), left precentral gyrus (BA 6), and frontal eye fields (BA 8) in individuals with delusions and more accelerated atrophy in the temporal middle gyri (BA 20 and 21, respectively) when compared to individuals without delusions (Qian, Schweizer, et al., 2019a).

In a longitudinal study of AD and delusions, regional gray matter decreases were found in the insula, precuneus, cerebellum, superior temporal gyrus, right posterior cingulate, thalamus, and left parahippocampal gyrus in individuals who developed delusions (Fischer & Sweet, 2016). Delusions of misidentification and mixed delusions were also related to reduced cortical volume bilaterally in the parahippocampal gyrus (McLachlan et al., 2018). In addition, treatment response to risperidone (for delusions) was significantly associated with larger volumes in the temporal lobe and limbic system (e.g., left amygdala and left parahippocampal gyrus) (Jeong et al., 2021). In the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, individuals who subsequently developed delusions had gray matter loss in the bilateral parahippocampal gyri and left hippocampus, right anterior cingulate cortex, and the posterior regions of the default mode network (DMN) (Manca et al., 2022). Delusions across multiple dementias were related to gray matter reductions in the dorsolateral frontal lobes, specifically the superior frontal gyrus and the right posterior lateral temporal lobe (Graff-Radford et al., 2012a). Delusions in Alzheimer's disease

appear to relate to unique cortical changes, namely in the frontal lobe as well as the temporal regions and limbic system, and subcortical areas relating to the dopaminergic pathways, all of which are not explained by AD alone. However, the exact mechanisms and etiology of these cortical alterations are still not fully understood. See Table 2 for more specific details.

The combination of a structural study with the examination of the genetic effect from the APOE ε4 allele will add to our understanding of the mechanisms by which this allele relates to delusions in AD and will inform treatment options for individuals with delusions by highlighting a neural underpinning of the symptom. Our hypothesis was that the ε4 allele has a pleiotropic effect, relating to multiple symptoms and clinical phenotypes, in both AD cognitive status and presence of delusions by way of gray matter volume in the CA1 subfield. We hypothesize that this effect is moderating two pathways 1) the relationship between CA1 volume and the presence of delusions and 2) the relationship between CA1 volume and AD cognitive status.

Table 2. Review of Structural Imaging Studies of Alzheimer's disease and Delusions

Study	Sample Size	Delusion assessment	Delusion Type	Direction of Findings	Imaging phenotype associated with delusions	Notes
(Fischer & Sweet, 2016)	MCI (7); AD (17)	NPI-Q	All	↓ in GM	L precuneus, insula, cerebellum, L superior temporal gyrus, L parahippocampal, R thalamus, R posterior cingulate	Longitudinal study
(Graff-Radford et al., 2012b)	DLBD (5); AD (6); bvFTD (3); D-(14)	UPDRS-TD	Othello syndrome	D+ < D-	Dorsolateral frontal lobes, superior frontal gyri, R posterior lateral temporal lobe	
(Qian, Schweizer, et al., 2019b)	AD (59); D+ (23), D- (36)	NPI-Q	Not specified	↓ in GM	Precentral and middle frontal gyri, SMA	Significant delusion × time interaction
(Serra et al., 2010b)	AD (27) MCI (19) HC (23)	NPI-12	All	↓ in GM	R hippocampus	5% D+
(Whitehead et al., 2012)	AD (113); D+ (23)	NPI	Paranoid	↓ in GM	L medial orbitofrontal, L superior temporal, L insula	Results only in females

All results used T1 scans. MCI: mild cognitive impairment; AD: Alzheimer's disease; DLBD: Dementia with Lewy Body disease; bvFTD: behavioral variant of Frontotemporal dementia; D+: individuals with delusions; D-: individuals without delusions; NPI-Q: Neuropsychiatric Inventory-Questionnaire; UPDRS-TD: Unified Parkinson's Disease Rating Scale-Tremor Dominant; L: left; R: right; GM: gray matter.

AIM I: EXAMINE THE RELATIONSHIP BETWEEN CA1 VOLUME, PRESENCE OF DELUSIONS, AND APOE ε4 STATUS

2.1 Aim and hypothesis

The overlap in gray matter alterations identified in the hippocampus, specifically in the CA1 region, in AD, delusions, and APOE ε4 status indicate potential support for an association between ε4 status and delusions. The goal of this project was to understand the relationship between the CA1 structure and the ε4 allele and determine if that relationship moderates the presence of delusions in AD. In this study, the first aim was to examine the relationship between the CA1 volumes and APOE ε4 status in individuals with delusions, and to determine if that relationship was significantly different from individuals without delusions.

We hypothesized that smaller CA1 volumes would relate more strongly to presence of delusions in those with the ε4 allele(s) when compared to those without an ε4 allele. We hypothesized the same moderation effect would be identified between the relationship of CA1 volume, AD cognitive status, and the APOE ε4 status such that in those individuals with ε4 allele(s), small CA1 volumes would relate to worse AD cognitive status (as measured by the MMSE). More specifically, we hypothesized that individuals with delusions would have smaller CA1 volumes compared to individuals without delusions and that CA1 volumes would be moderated by the APOE ε4 status.

2.2 Methods

2.2.1 Participants

For this study, we utilized two open-access Alzheimer's disease and aging datasets. The Open Access Series of Imaging Studies (OASIS) is a large-scale collection of imaging data from several projects originally collected to examine the effects of healthy aging and Alzheimer's disease (AD) (Marcus et al., 2007). The data were collected over the course of 30 years including both cognitively normal adults and adults at various stages of cognitive decline. The current project used the OASIS-3 data release that included structural MR sessions, clinical assessments, and biological data (LaMontagne et al., 2019). There were a total of 1,377 participants aged 42 to 95 years old, including cognitively typical individuals (N = 755) and individuals diagnosed with early-stage AD dementia and other various stages of cognitive decline (N = 622) (LaMontagne et al., 2019). This most recent data release has structural (MRI) imaging data, neuropsychological testing, including the Neuropsychiatric Interview-Questionnaire (NPI-Q), and APOE genotyping completed (LaMontagne et al., 2019). Data were collected under the approval of local institutional review boards and all participants provided informed consent. The recruitment and informed consent process have both been previously described in the literature (LaMontagne et al., 2019).

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal multicenter study designed to develop biomarkers for Alzheimer's disease by examining clinical, imaging, genetic, and biochemical correlates of the disease's progression (Weiner et al., 2010). Through the multiple study arms, ADNI has enrolled roughly 400 individuals with AD, 1,000 individuals with mild cognitive impairment, and 480 cognitively typical individuals (Weiner et al., 2010, 2017).

For both datasets, there were initial diagnoses assigned at the screening visit. These diagnoses were confirmed at the baseline visit using clinical and neuropsychological testing.

Diagnoses were potentially re-classified, if applicable, upon subsequent visits. In both datasets, Alzheimer's disease diagnoses were diagnosed clinically and characterized using the Clinical Dementia Rating (CDR) scale (Morris et al., 2001). ADNI stated that participants needed to have a score of greater than 0.5 to be classified as AD and OASIS used a score of greater than zero (0). For the purposes of this study, the diagnoses listed in the ADNIMERGE.csv were used for the ADNI dataset and the diagnoses listed in "dx1" column were used for the OASIS-3 dataset as of August 1, 2022. In total, there were 206 individuals from the ADNI dataset and 279 from the OASIS dataset that had 1). an Alzheimer's diagnosis and 2). a high quality T1 structural MRI image. See Table 3 for the participant information as it relates to this current study.

Table 3. Alzheimer's Disease (AD) Participant Information by Study.

		OASIS3	**ADNI**	**Total**
N		279	206	485
Age (M; SD)		74.02 (8.09)	74.85 (7.67)	74.34 (7.89)
Males (%)		138 (49.46%)	103 (50%)	241 (49.69%)
[#]Race (%)	Caucasian	222 (85.06%)	182 (93.81%)	404 (88.79%)
	African-American	39 (14.94%)	6 (3.09%)	45 (9.89%)
	Asian	0 (0%)	4 (2.06%)	4 (0.88%)
	Selected > 1 Race	0 (0%)	2 (1.03%)	2 (0.439%)
APOE ε4 alleles	0 ε4 alleles	119	33	152
	1 1 ε4 allele	137	135	272
	2 ε4 alleles	23	38	61
Delusions (%)		35 (12.54%)	38 (18.45%)	73 (15.05%)
MMSE (M; SD)		21.56 (6.28)	23.52 (2.69)	22.43 (5.09)

[#]Missing reports from both OASIS (N = 18) and ADNI (N = 12). Percentages calculated based off total reported values.

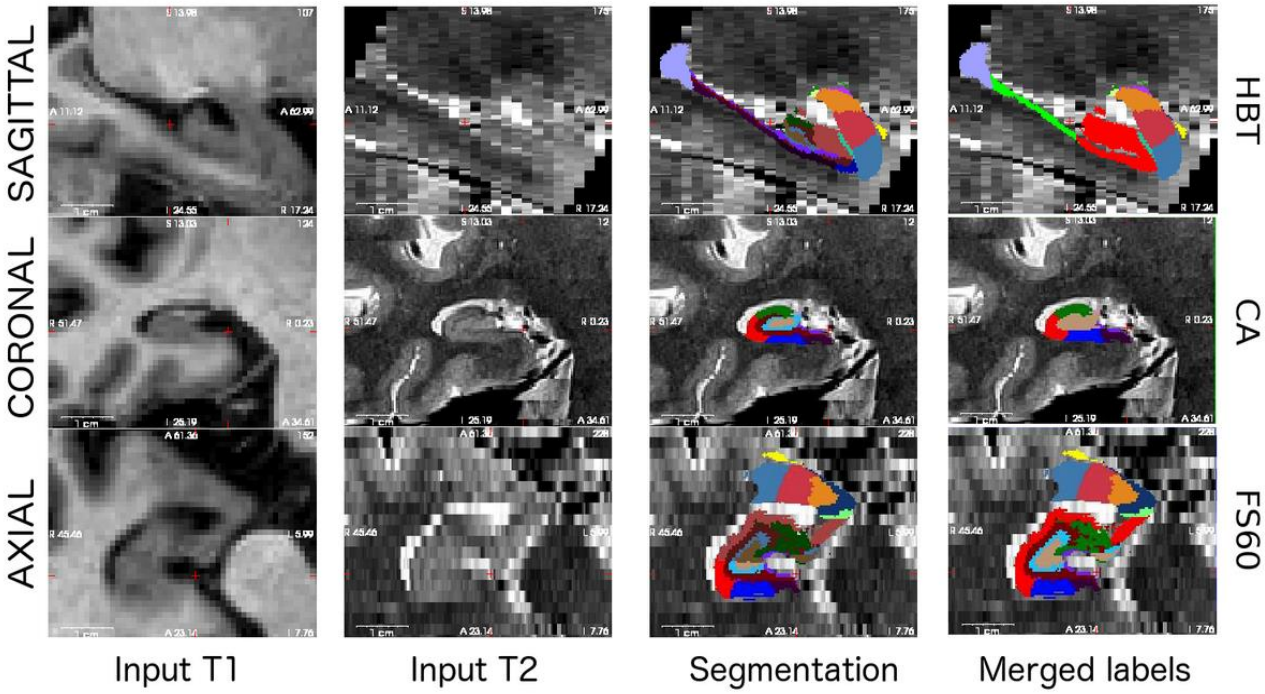
2.2.2 Neuroimaging data

MRI images from both datasets had already been collected and all images had been graded for quality assurance by the ADNI investigators. The MRI scans are all T1-weighted MR images. For ADNI, MRI acquisition was completed following the ADNI acquisition protocol (Jack et al., 2008). Briefly, advanced imaging (diffusion imaging, resting state fMRI, or arterial spin labeling) was included depending on scanner manufacturer. The primary acquisition for the T1 sequence was an accelerated sagittal IR-FSPGR (Repetition Time (TR) = 7.36 ms, Echo Time (TE) = 3.05 ms, Inversion Time (TI) = 400 ms, Flip Angle (FA) = 11 degrees, Voxel Size (VS) = 1 X 1 X 1 mm, Matrix Size = 256 X 256, Field of View (FOV) = 256, 196 slices). For OASIS, MRI acquisition was completed following the OASIS protocol (LaMontagne et al., 2019). All scans were conducted by the Knight Alzheimer Research Imaging Program at Washington University. OASIS included T1-weighted MR images that were collected on either Siemens 3T (using a 20-channel head coil) or 1.5T (using a 16-channel head coil) scanners. More details on the OASIS MRI protocol can be found on their website (https://www.oasis-brains.org).

Preprocessing of imaging data. Both ADNI and OASIS are longitudinal datasets that have collected multiple scans from participants. For the purposes of this study, only the most recent MRI scans (determined by visit date) were utilized for analysis. T1-weighted structural MRI data from both the ADNI and OASIS datasets were preprocessed with the FreeSurfer software suite v7.1.1 (https://surfer.nmr.mgh.harvard.edu/). The FreeSurfer automated pipeline consists of several processing steps, including skull stripping, Talairach transformation, subcortical structure labelling, surface extraction, spherical registration, and cortical parcellation. In brief, T1-weighted images are motion-corrected and non-brain tissue is removed using a hybrid watershed/surface deformation procedure. The images are automatically registered to Talairach space and segmented

into subcortical white matter and gray matter structures. This automated process and protocol have been previously described in the literature (Dale et al., 1999; Fischl et al., 2002). To assure data quality, all MRI images were run through FreeSurfer's quality assessment (QA) tool (https://surfer.nmr.mgh.harvard.edu/fswiki/QATools) and the images with poor QA (ADNI: N = 3; OASIS: N = 19) were removed from all analyses. The T1-weighted MR images were run through hippocampal segmentation (Iglesias et al., 2015). This tool uses a probabilistic atlas built with ultra-high resolution ex vivo MRI data (~0.1 mm isotropic) to produce an automated

Figure 2. Multi-slice view of hippocampal segmentation in Freesurfer v7.



segmentation of the hippocampal substructures (see Fig. 2 originally from the Freesurfer website: https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala). For the purposes of this Aim, we followed the guidelines and cautions outlined in (Wisse et al., 2021), and only examined the CA1 subfield as a sole region of interest. The *CA1-head* and *CA1-body* volumes were summed to generate a total CA1 volume for both the left and right CA1.

2.2.3 Genotyping

For the ADNI APOE genotyping, APOE genotyping was performed at the time of participant enrollment. The two SNPs (*rs*429358, *rs*7412) that define the ε2, ε3, and ε4 alleles, are not on the Human610-Quad BeadChip, and therefore were genotyped using DNA extracted by Cogenics from a 3 mL aliquot of EDTA blood. For the OASIS APOE genotyping, APOE genotyping was performed with blood samples using PCR amplification of a 244-bp fragment followed by restriction enzyme Hhal digest (Hixson & Vernier, 1990; LaMontagne et al., 2019). Genomic DNA was extracted from blood samples using QIAmp DNA blood mini kits from Qiagen Inc. (Valencia, CA). APOE genotyping was performed using PCR amplification of a 244-bp fragment followed by restriction enzyme HhaI digest22.

2.2.4 Assessments

MMSE. Both datasets included the Mini-Mental State Exam (Folstein et al., 1975) , an 11-question test designed to test various aspects of cognitive functioning in the elderly. For those with a college education, a score below 24 is considered abnormal and possible mild cognitive impairment. For the purposes of this study, we used the total MMSE score as an indicator for cognitive status as it relates to Alzheimer's disease presentation. In the ADNI dataset, the average MMSE score was 23.52 (SD = 2.69) and the range was between 17 and 30. In the OASIS dataset, the average MMSE score was 21.56 (SD = 6.28) and the range was between 1 and 30 (all zeros were removed from analyses).

NPI-Q. A common assessment for psychosis utilized with individuals with AD is the Neuropsychiatric Interview (NPI) and the adapted, shortened version, the Neuropsychiatric Interview-Questionnaire (NPI-Q) (Cummings, 1994; Kaufer et al., 2000). The NPI has one

question regarding delusions, “Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Or has he/she said that family members are not who they say they are or that the house is not their home?”. If the patient or caregiver answers “yes” then there are nine follow-up questions asking about the type of delusion (all focused on paranoia or persecution). The NPI-Q has one question regarding delusions, “Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?”. For the purposes of this study, we used either of the responses to the above questions (and the subsequent Likert scales of severity and distress if answered “yes”) to quantify the presence of delusions (yes or no) in our sample. In the ADNI dataset, there were 39 individuals with AD who endorsed delusions on either one or both scales. The OASIS dataset only had the NPI-Q completed for participants and there were 40 individuals with AD who endorsed delusions.

2.2.5 Statistical Analyses

We used two hierarchical regression models (one logistic and one linear) to examine if the APOE ε4 allele is moderating the relationship between 1) CA1 volume and the presence of delusions and 2) CA1 volume and Alzheimer’s disease cognitive status (as measured by the MMSE). The analyses were performed in SPSS v28.0.1.1 (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) as a block design with age, sex, and site in Block 1, number of APOE ε4 alleles (0, 1, or 2) in Block 2, CA1 volume and total hippocampal volume in Block 3, the interaction between centered CA1 volume and centered number of APOE ε4 alleles (0, 1, or 2) in Block 4. The outcome for the first model was the presence of delusions (binary coded: 0 (absent) or 1 (present)). The interaction between CA1 volume and number of APOE ε4 alleles was calculated by first centering CA1 volume and allele number

around their mean and then computing the product term from those centered predictor variables. The outcome for the second model was the Mini-Mental State Exam scores (using the same block design as described above). To control for the two sets of analyses, Bonferroni correction was applied ($\alpha < 0.025$ (.05/2)) to our significance threshold for all analyses.

a-priori Power analysis. We ran power analyses to confirm that the sample sizes will yield results with sufficient effect sizes. For a moderate effect size (0.20 for *F* test), α level corrected for two tests at 0.025, the minimal total sample size to achieve power over 90% (assuming equal sample size in each group) is 108 (54 for each group) (Faul et al., 2007).

2.3 Results

In the ADNI dataset, there were 206 individuals with an Alzheimer's disease (AD) diagnosis. Of those 206 individuals, 38 individuals endorsed delusions. In the OASIS dataset, 279 individuals with a primary Alzheimer's disease (AD) diagnosis. Of those 279 individuals, 35 individuals endorsed delusions. The two groups of individuals, those with delusions and those without delusions, did not significantly differ on the covariates of age, sex, education attainment, and MMSE scores. There was also no significant difference in APOE ε4 status (χ^2 (2) = 5.076, *p* = .079) between the two groups. The groups did significantly differ on race distribution (χ^2 (3) = 13.933, *p* = .003) with individuals without delusions having significantly more individuals identifying as Caucasian. See Table 4 for more details on group differences.

Table 4. Group Differences for AD Individuals with and without Delusions.

	Delusions	**No Delusions**	***t***	**χ^2**	***p***
N	73	392	__	__	__
Age (M; SD)	74.80 (8.16)	74.25 (7.85)	-0.547	__	.585
Sex (M %)	33 (45.21%)	207 (52.81%)	—	1.424	.233

Race (Caucasian %)	55 (75.34%)	336 (85.71%)	__	13.933	.003*
MMSE	22.80 (3.88)	22.37 (5.28)	-0.803	__	.258
Education	14.97 (3.02)	15.11 (3.12)	0.346	__	.365
Left Hippocampal volume (mm^3)	2506.31 (434.55)	2563.46 (461.69)	0.982	__	.163
Right Hippocampal volume (mm^3)	2593.31 (483.76)	2736.20 (523.02)	2.172	__	.015*
Left CA1 total volume (mm^3)	477.98 (83.47)	488.30 (94.26)	0.876	__	.191
Right CA1 total volume (mm^3)	495.46 (94.67)	527.89 (107.84)	2.407	__	.008*
APOE alleles	18 0 ε4 allele 37 1 ε4 allele 13 2 ε4 alleles	152 0 ε4 allele 196 1 ε4 allele 46 2 ε4 alleles	__	5.076	.079

*p value passing Bonferroni corrected $\alpha < .025$.

Delusions. The presence of delusions were not significantly correlated with the left CA1 (r = -.040, p = .382) volume nor the left whole hippocampus volume (r = -.045, p = .327) but were significantly corrected with the right CA1 volume (r = -.110, p = .016) and right whole hippocampus volume (r = -.099, p = .030). See Figure 3 for the left CA1 volume distribution among individuals with delusions and Figure 4 for the right CA1 volume distribution. Logistic regression in a block design was used to analyze the relationship between CA1 volumes and APOE ε4 allele status on the presence of delusions. Age, sex, and site were included in Block 1, APOE ε4 allele status was included in Block 2, CA1 volume and whole hippocampal volume were in Block 3, APOE ε4 allele and CA1 volume interaction was Block 4.

For the left CA1, none of the blocks resulted in a significant model. There was an improvement in the predictive power of the model with the addition of Block 2, the APOE ε4 allele (χ^2 = 3.28, p = .070) but the total model did not reach significance (χ^2 = 72.87, p = .054). The additions of Blocks 3 and 4 did not improve the predictive power of the model. See Table 5

for change in R^2 for each additional Block and Table 6 for the total model results. In the final model, there was no significant association between the left CA1 volume and the presence of delusions (OR = 0.999 [95% CI: 0.989, 1.009]; $p = .870$) and there was no significant association in the interaction between the left CA1 volume × APOE ε4 allele status and the presence of delusions (OR = 1.000 [95% CI: 0.994, 1.006]; $p = .953$).

Table 5. Aim I: Cox and Snell R^2 and Total Model χ^2 Change with Each Block Design.

	Cox and Snell R^2	**Block χ^2**	***p***	**Total model χ^2**	***p***
Left CA1					
Age, Sex, Site	.165	69.59	.075	69.59	.075
APOE ε4 allele	.172	3.28	.070	72.87	.054
Left CA1 & Whole hippocampus	.172	0.22	.895	73.09	.074
Left CA1 × APOE ε4 allele	.172	0.003	.953	73.092	.953
Right CA1					
Age, Sex, Site	.165	69.59	.075	69.59	.075
APOE ε4 allele	.172	3.28	.070	72.87	.054
Right CA1 & Whole hippocampus	.176	1.82	.402	74.69	.058
Right CA1 × APOE ε4 allele	.180	2.34	.126	77.03	.048

*p value passing Bonferroni corrected $\alpha < .025$. No results reached significance.

For the right CA1, each additional block moderately improved the predictive power of the model, but no model reached significance. The same association with Block 2, the APOE ε4 allele showed a moderate, but not significant, association with the presence of delusions ($\chi^2 = 3.28$, $p = .070$) with the total model not reaching significance ($\chi^2 = 72.87$, $p = .054$). Block 3, the right CA1 and right whole hippocampus, resulted in an improvement in the model ($\chi^2 = 74.69$, *p*

= .058). And the interaction between the right CA1 and the APOE ε4 allele status also improved the model with an increased R^2 but the significance of the total model did not survive Bonferroni correction (χ^2 = 77.03, p = .048). See Tables 5 and 6 for more details.

Individuals with one or more APOE ε4 alleles were 1.58 times more likely to present with delusions but this association did not reach significance (95% CI [0.945, 2.655]; p = .081). For the right CA1 volume, there was no significant association between CA1 volume and the presence of delusions (OR = 0.993 [95% CI: 0.983, 1.003]; p = .161). There was no significant association in the interaction of the right CA1 volume × APOE ε4 allele status and the presence of delusions (OR = 1.004 [95% CI: 0.999, 1.009]; p = .132). See Figures 5 and 6 for more details on the APOE ε4 allele interaction and CA1 volumes within individuals with delusions.

Figure 3. Left CA1 Volumes Across Individuals with and without Delusions.

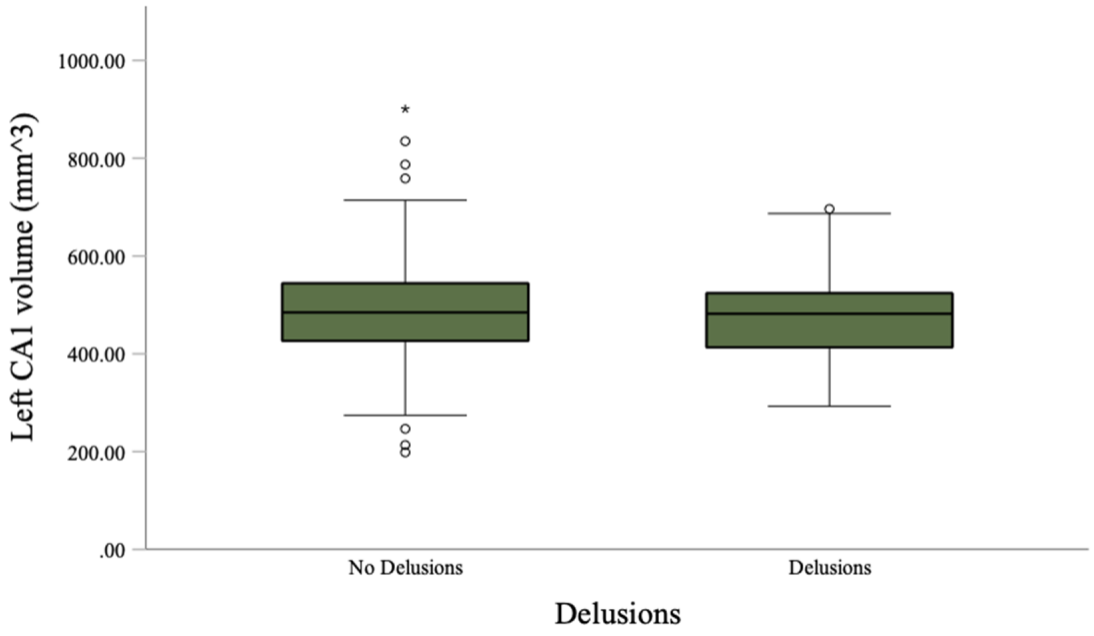


Fig 3. Results showed no significant difference between individuals with delusions and individuals without delusions in the left CA1 volume (t = 0.876, p = .191).

Figure 4. Right CA1 Volumes Across Individuals with and without Delusions.

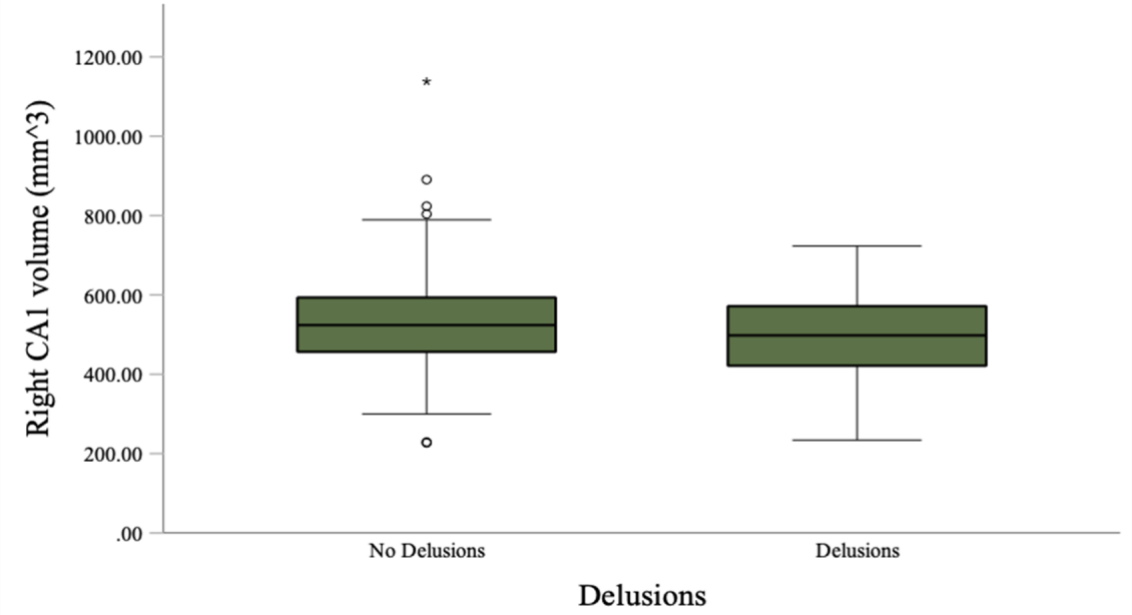


Fig 4. Results showed individuals with delusions had significantly less right CA1 volumes than individuals without delusions (t = 2.407, p = .008). However, this association was not significant once accounting for age, sex, and site.

Table 6. Logistic Regression Block 4 Results Examining Delusions and CA1 Volumes.

	B	Wald	OR	*p*
Left CA1				
Age	0.036		1.037	.134
Sex	-0.493		0.611	.160
Site		20.328		1.00
APOE ε4 allele	0.481		1.618	.065
CA1	-0.001		0.999	.870
Whole hippocampus	0.000		1.000	.759
APOE × CA1 Interaction	0.000		1.000	.953
Right CA1				
Age	0.025		1.026	.269
Sex	-0.458		0.633	.198
Site		21.228		1.00
APOE ε4 allele	0.460		1.584	.081
CA1	-0.007		0.993	.161
Whole hippocampus	0.001		1.001	.207
APOE × CA1 Interaction	0.004		1.004	.132

Site was included as a categorical variable (df = 52). OR: Odds Ratio. $^{*}p$ value passing Bonferroni corrected $\alpha < .025$. No results reached significance.

Figure 5. APOE alleles and left CA1 volume interaction on the presence of delusions.

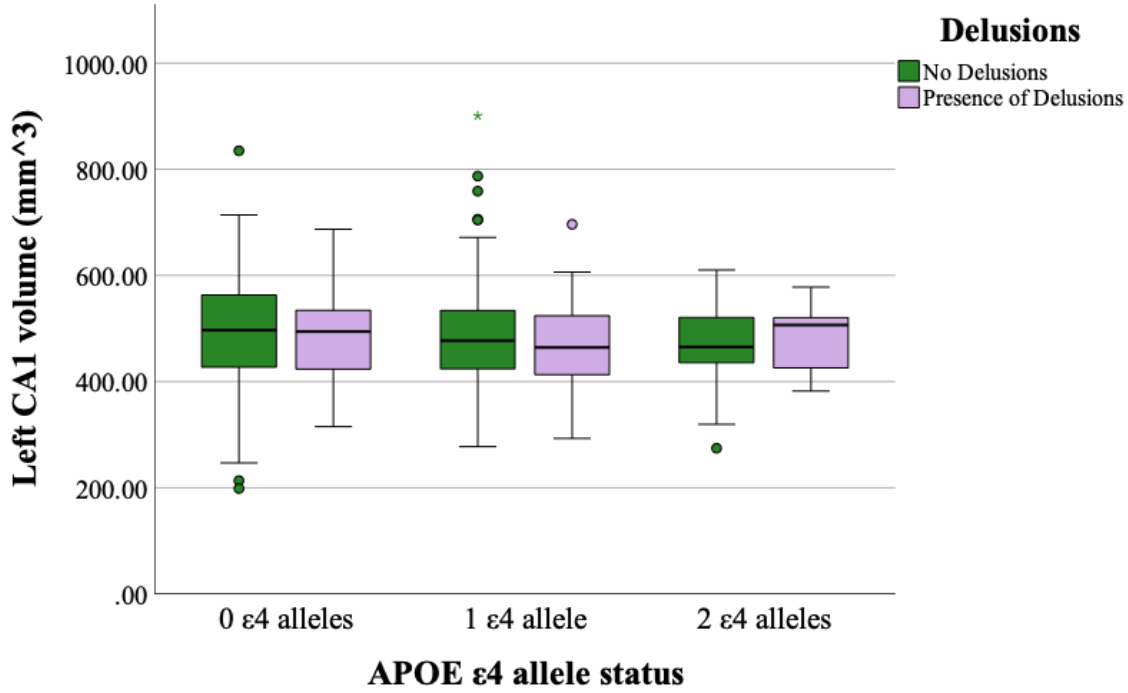


Fig 5. Results showed there was no significant interaction between APOE alleles and left CA1 volumes between individuals with delusions and individuals without delusions.

Figure 6. APOE alleles and right CA1 volume interaction on the presence of delusions.

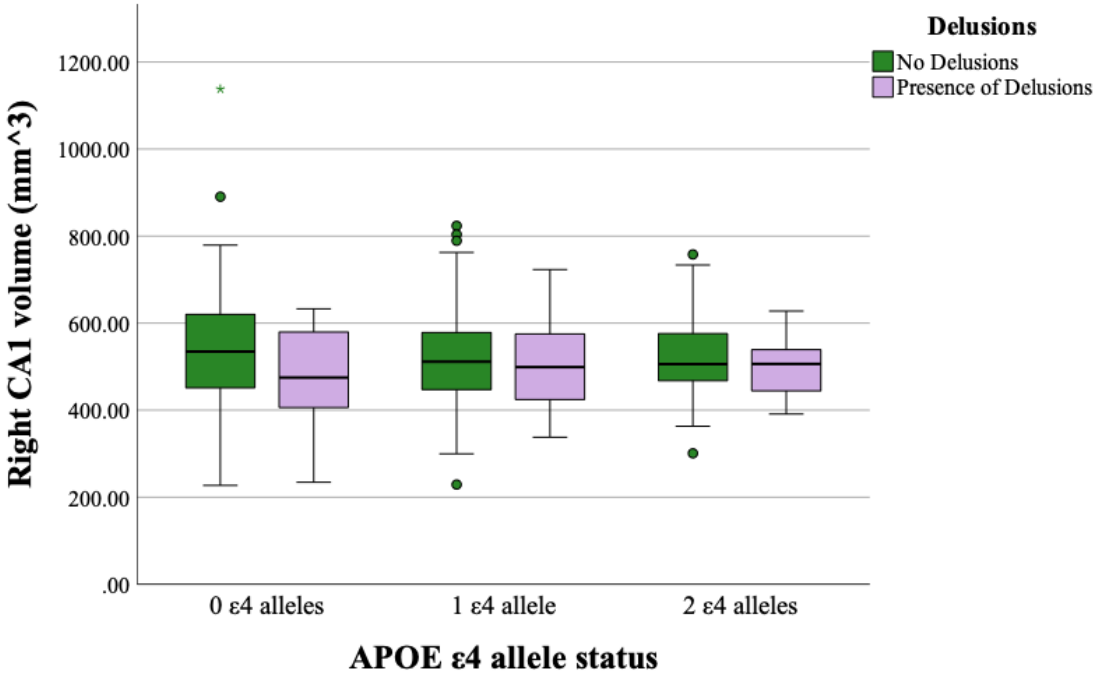


Fig 6. Results showed the interaction between APOE alleles and right CA1 volumes showed a slight increase in the average right CA1 volumes of individuals presenting with delusions with each increase of APOE ε4 allele status but this interaction did not survive correction.

Results of the paired *t*-test comparing the CA1 subfields, head and body, in both the left and right CA1 volumes found a significant difference unilaterally in the right CA1 head (t = 2.33, p = .010) and the right CA1 body (t = 2.084, p = .019). The CA1 subfields were also examined separately using the same logistic regression block model above and there were no significant associations with either the left (head: OR = 1.007 (95% CI [0.989, 1.026], p = .444; body: OR = 0.995, 95% CI [0.984, 1.005], p = .332) nor the right subfields (head: OR = 0.993, 95% CI [0.98, 1.002], p = .138; body: OR = 0.985, 95% CI [0.94, 1.007], p = .176) and the presence of delusions.

In additional post-hoc logistic regression block design models, we analyzed the relationship between CA1 volumes and APOE ε4 allele status as a binary factor (presence or absence of ε4 alleles) on the presence of delusions. The same models were used with age, sex, and site included in Block 1, binary APOE ε4 allele status included in Block 2, CA1 volume and whole hippocampal volume were in Block 3, and APOE ε4 allele × CA1 volume interaction was Block 4.

For the left CA1, there was no significant association between CA1 volume and the presence of delusions (OR = 0.999 [95% CI: 0.987, 1.011]; p = .886) and there was no significant association in the interaction between the left CA1 volume × APOE ε4 allele status and the presence of delusions (OR = 1.000 [95% CI: 0.993, 1.007]; p = .978). For the right CA1, the addition of Block 4, the interaction between APOE presence and right CA1 volumes, reached significance (R^2 = .180; χ^2 = 76.93, p = .049), however, this association did not survive Bonferroni correction. There was a significant association between right CA1 volumes and the presence of delusions (OR = 0.988 [95% CI: 0.977, 1.000]; p = .042), however, this association also did not survive correction for multiple testing ($\alpha < 0.025$). There was no significant

association in the interaction between the right CA1 volume × APOE ε4 allele presence and the presence of delusions (OR = 1.007 [95% CI: 0.999, 1.014]; p = .085). See Supplemental Table 1 for more details on the block design results for binary APOE ε4 allele presence.

MMSE. There were no significant differences between individuals without delusions (M = 22.37, SD = 5.28) and individuals with delusions (M = 22.80, SD = 3.88) on MMSE scores (t = -0.803, p = .212). MMSE scores were significantly correlated with left CA1 volumes (r = .130, p = .005) and left (r = .155, p = 8.15E-4) and right (r = .108, p = .021) whole hippocampus volumes and right CA1 volumes (r = .095, p = .041) but this last interaction did not survive Bonferroni correction. There was a significant difference in APOE ε4 allele status (F(2) = 3.371, p = .035) and MMSE scores but this interaction also did not survive Bonferroni correction (α < 0.025).

Linear regression block design models were used to analyze the relationship between CA1 volumes and APOE ε4 allele status on MMSE scores. For the left CA1 volume, only the addition of Block 3 (left CA1 volume and left hippocampus) improved the predictiveness of the model (final adjusted R^2 = .018; F(6) = 2.139, p = .048) but this association did not survive multiple-test correction. The addition of Block 4 (the interaction between left CA1 and APOE ε4 allele status) did not improve the model (F(7)= 1.838, p = .079). For the right CA1 volume, only the addition of Block 3 (right CA1 volume and right hippocampus; F(6) = 1.571, p = .154) improved the predictiveness of the model adjusted (R^2 = .009) but none of the block models reached significance. See Table 7 for more details on the adjusted R^2 of each model.

Table 7. Adjusted R^2 Block Design Results for Left and Right CA1 on MMSE Scores.

	Adjusted R^2	**F**	**Mean Square**	***p***
Left CA1				
Age, Sex, Site	.005	1.601	41.174	.189

APOE ε4 allele	.005	1.432	36.848	.223
Left CA1 & whole hippocampus	.018	2.139	54.295	.048
Left CA1 × APOE ε4 allele	.015	1.836	46.712	.079
Right CA1				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele	.005	1.432	36.848	.223
Right CA1 & whole hippocampus	.009	1.571	40.239	.154
Right CA1 × APOE ε4 allele	.008	1.430	36.668	.192

*p value passing Bonferroni corrected $\alpha < .025$. No results reached significance.

There were no significant associations between MMSE and either the left CA1 volume (β = -0.105, p = .503) or the right CA1 volume (β = -0.024, p = .892). The interaction of left CA1 volume × APOE ε4 allele status (β = -0.012, p = .827) was not significantly associated with MMSE. See Figure 7 for more details of the interaction. The interaction of the right CA1 volume × APOE ε4 allele status was also not significantly associated (β = 0.042, p = .441) with MMSE score. See Table 8 for more details and see Figure 8 for the spread of right CA1 volumes across MMSE scores.

Figure 7. Interaction of APOE ε4 allele and Left CA1 volume on MMSE Scores.

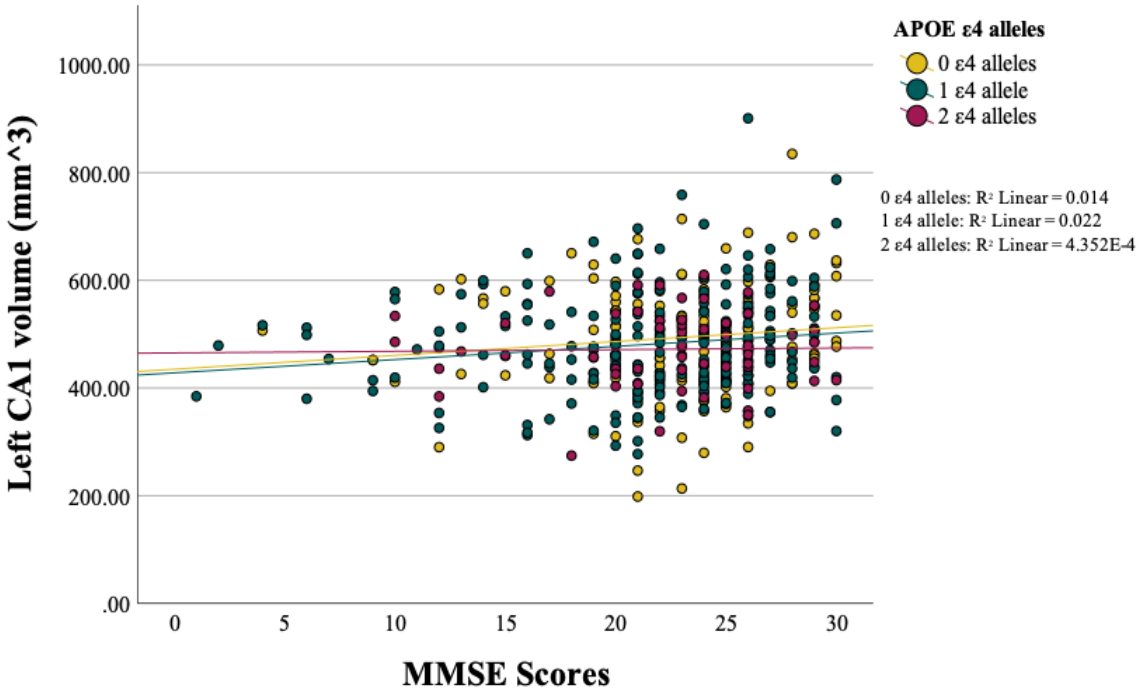


Fig 7. Results showed the interaction of APOE ε4 alleles and Left CA1 volumes was not significantly associated with the spread of MMSE scores.

Table 8. Linear Regression Block 4 Results Examining MMSE Scores and CA1 Volumes.

Left CA1	**β**	***t***	***p***
Age	-0.004	-.079	.937
Sex	0.010	0.193	.847
Site	-0.115	-2.210	.028
APOE ε4 allele	-0.030	-0.571	.568
Left CA1 (mm^3)	-0.105	-0.670	.503
Left whole hippocampus	0.238	1.498	.135
APOE ε4 allele × left CA1	-0.012	-0.218	.827
Right CA1			
Age	-0.031	-0.572	.567
Sex	0.001	0.022	.982
Site	-0.108	-2.080	.038
APOE ε4 allele	-0.034	-0.637	.525
Right CA1 (mm^3)	-0.024	-0.136	.892
Right whole hippocampus	0.137	0.772	.441
APOE ε4 allele × Right CA1	0.042	0.771	.442

*p value passing Bonferroni corrected $\alpha < .025$. No results reached significance.

Figure 8. Interaction of APOE ε4 allele and Right CA1 volume on MMSE Scores.

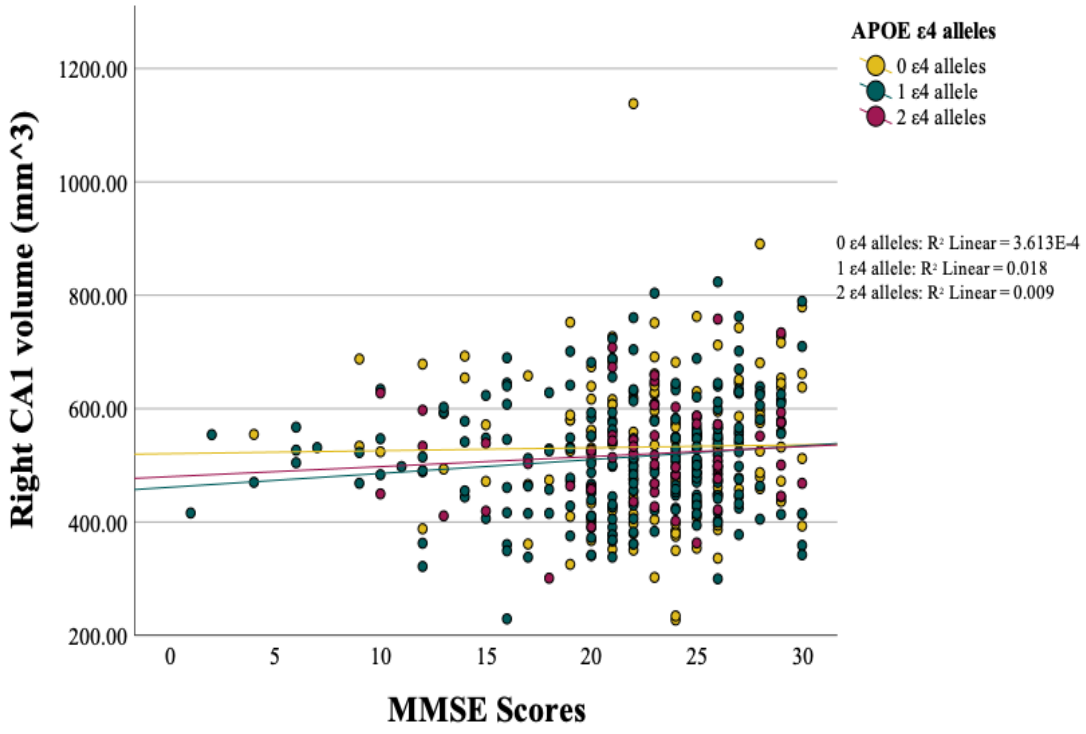


Fig 8. Results showed that the interaction of APOE ε4 alleles and right CA1 volumes was not significantly associated with the spread of MMSE scores.

In the Pearson's correlation models, MMSE scores were compared to the left and right CA1 subfield volumes, head and body. MMSE was positively correlated with both the left CA1 head (r = .126, p = .007) and the left CA1 body (r = .016, p = .023) and with the right CA1 head (r = .093, p = .046) but this last association did not survive Bonferroni correction. In linear regression block design models, we analyzed the relationship between the left and right CA1 subfield volumes, head and body, and APOE ε4 allele status on MMSE scores. The additional CA1 subfields did not significantly change the original models of CA1 volumes. In the left CA1 head model, the addition of Block 3 (left CA1 head volume and left hippocampus) improved the model (adjusted R^2 = .018; $F(6)$ = 2.146, p = .048) but none of the models reached Bonferroni correction significance. Neither the right CA1 head nor right CA1 body block designs were significant. See Supplemental Table 2 for more details on these CA1 subfields.

Last, we analyzed the relationship between CA1 volumes and APOE ε4 allele status as a binary factor (presence or absence of ε4 alleles) on MMSE Scores. For the left CA1 volumes, Block 3 (left CA1 and left hippocampus) was the most predictive model (adjusted R^2 = .024; $F(6)$ = 2.566, p = .019) and survived Bonferroni correction ($\alpha < 0.025$). See Table 9 and Figure 9 for more details. For the right CA1 volumes, each block improved the predictiveness of the model but none of the blocks reached significance.

Table 9. Linear Regression Block Design Results for CA1 Subfields on MMSE Scores and binary APOE ε4 alleles.

	Adjusted R^2	**F**	**Mean Square**	***p***
Left CA1				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele (binary)	.013	2.250	57.381	.063
Left CA1 & whole hippocampus	.024	2.566	64.691	.019*
Left CA1 × APOE ε4 allele (binary)	.022	2.205	55.723	.033

Right CA1				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele (binary)	.013	2.250	57.381	.063
Right CA1 & whole hippocampus	.016	2.029	51.600	.061
Right CA1 × APOE ε4 allele (binary)	.015	1.804	45.941	.085

*p value passing Bonferroni corrected $\alpha < .025$.

Figure 9. Significance of Presence of APOE ε4 allele and Left CA1 volume on MMSE Scores.

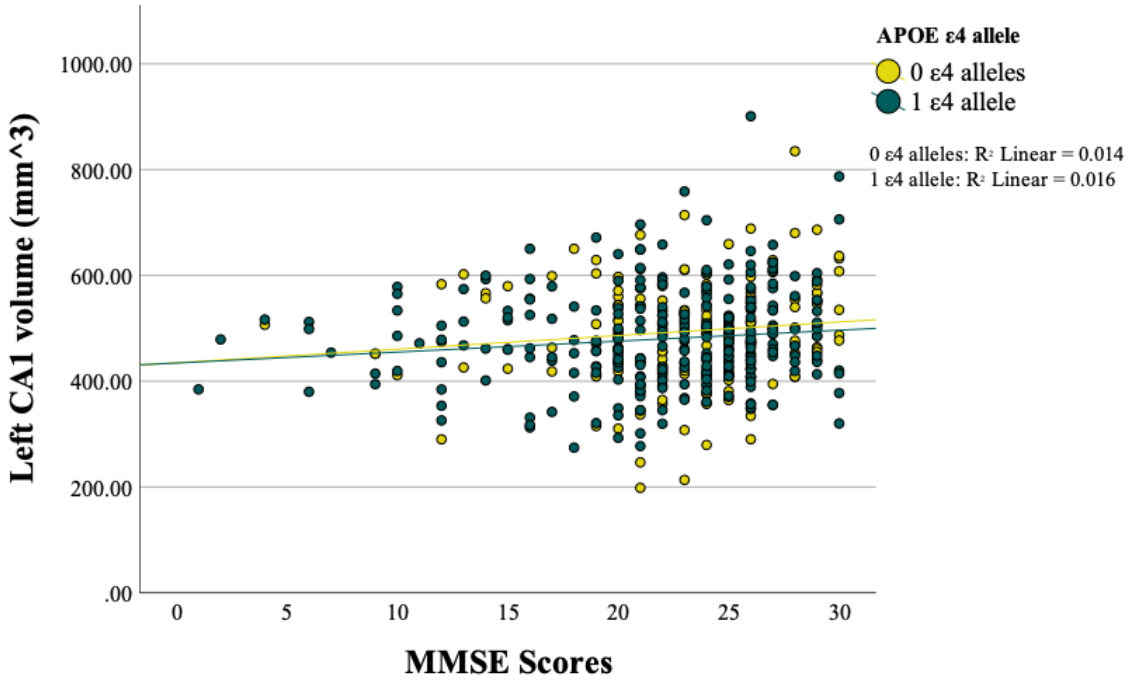


Fig 9. Results showed that the Left CA1 volumes were significantly associated with MMSE scores and that relationship was moderated by APOE ε4 allele presence.

AIM II: CONFIRMATION OF THE RELATIONSHIP BETWEEN CA1 VOLUME, PRESENCE OF DELUSIONS, AND APOE ε4 ALLELE STATUS THROUGH HIGH-RESOLUTION T2 IMAGES

Hippocampal subfields are heterogeneous in cytoarchitecture and function (Chase et al., 2015; Eckermann et al., 2021; Small et al., 2011). Examination of subfield-specific changes allows for an accurate relationship of the subfield and its function or relationship to disease state. However, subregions of the hippocampus are especially difficult to accurately measure due to their small size and insufficient signal contrast with typical MRI acquisition. In addition, the resolution of hippocampus subfield segmentation from ~1 mm^3 MRI may be insufficient for valid visualization of the internal structures of the hippocampus, how the hippocampus is segmented (Wisse et al., 2021). Therefore, to build upon the findings from Aim I with more accurate segmentation, Aim II used the preprocessed high resolution (0.4x0.4x2 mm^3) T2 MRI images from ADNI3 data and the hippocampal segmentation completed by Dr. Paul Yushkevich at the University of Pennsylvania using the Automatic Segmentation of Hippocampal Subfields (ASHS; https://www.nitrc.org/projects/ashs). ASHS allows for automatic segmentation of the hippocampal subfields from the T1-weighted scan and T2-weighted images to obtain optimal segmentation (Wisse et al., 2016, 2021). Further details on the segmentation differences have been thoroughly described in the original paper and subsequent literature (Iglesias et al., 2016; Wisse et al., 2021).

3.1 Aim and hypothesis

We used the T2 MRI images from the ADNI3 dataset as confirmatory data to test the specificity of the CA1 volume change. In this aim, we re-tested the hypotheses from Aim I, that there is a moderating effect of the APOE ε4 allele on the relationships between CA1 volume and

presence of delusions and AD cognitive status while modeling the other hippocampal subfields. More specifically we examined if the CA1 volumetric differences were unique to its region or if the other hippocampal subfields (CA2 and CA3) also presented with volumetric changes in individuals with delusions. This approach allows for a more precise analysis of CA1 volume as a biological correlate of the APOE ε4 pleiotropic effect because we compared different subfields of the hippocampus. We utilized the extracted hippocampal subfields (CA1, CA2, and CA3) in the ADNI3 dataset for Aim II.

3.2 Methods

3.2.1 Participants

For Aim II, we used the coronal high-resolution T2 images from participants acquired at 3T scanners specifically focused on the medial temporal lobe (MTL) subregion. These images are intended to quantify changes in the hippocampal subfields and parahippocampal gyrus subregions. The ASHS volume data (version 2022-02-15) were downloaded from the ADNI website (https://ida.loni.usc.edu/). There were a total of 1978 volume entries from 1137 individuals. The most recent scan (determined by the scan date) was used for all subsequent analyses. Only confirmed Alzheimer's disease (AD) dementia diagnoses were included; there were a total of 99 individuals with AD dementia. There were 34 individuals who were included in both Aim I and Aim II. Presence of delusions was recorded by either the Neuropsychiatric Inventory (NPI) or the NPI-Questionnaire (NPI-Q). Of the 99 individuals, 12 endorsed delusions at the time of scan. Quality assurance (QA > 1) removed eleven total individuals from analyses. Participant information is listed in Table 10. The two groups (individuals with delusions and individuals without delusions) did not significantly differ in mean age, gender distribution, mean education attainment, or APOE ε4 allele distribution.

Table 10. Demographic Information from ADNI3.

	Delusions	No Delusions	*t*	χ^2	*p*
N	11	77	__	__	__
Age (M; SD)	71.69 (9.74)	70.38 (11.34)	-0.366	__	.358
Sex (Males %)	4 (36.36%)	44 (57.14%)	__	1.68	.195
Race (Caucasian %)	8 (72.72%)	72 (93.50%)	__	5.410	.067
MMSE	17.33 (6.63)	22.12 (4.81)	2.641	__	.005*
Education	16.89 (1.76)	15.75 (2.35)	-1.399	__	.083
APOE ε4 alleles	3 0 ε4 allele 5 1 ε4 allele 3 2 ε4 alleles	26 0 ε4 allele 35 1 ε4 allele 16 2 ε4 alleles	__	5.076	.079
ICV (M; SD)	1,241,878.55 (78,771.145)	1,329,247.69 (143,977.960)	3.027	__	.003*
Left CA1 volume (mm^3)	968.86 (247.88)	945.84 (251.51)	-0.284	__	.388
Right CA1 volume (mm^3)	962.13 (197.03)	938.16 (226.52)	-0.333	__	.370

AD: Alzheimer's disease; M: mean; SD: standard deviation; MMSE: Mini-Mental State Exam; ICV: intracranial volume. Race breakdown was as follows in delusion group: 8 Caucasian, 2 African American, 1 Asian; in non-delusion group: 72 Caucasian, 4 African American, and 1 Asian. **p* value passing Bonferroni corrected $\alpha < .025$.

3.2.2 Assessments

The same assessments from Aim I were utilized for Aim II. Refer to Chapter 2 for more information on the Neuropsychiatric Inventory-Questionnaire (NPI-Q) and Mini-Mental State Exam (MMSE).

3.2.3 Image Processing

Volumetric measurements of subregions of the medial temporal lobe were generated by applying ASHS software (https://sites.google.com/site/hipposubfields/) to the hippocampal T2-

weighted MRI scans of the ADNI3 subset (Yushkevich et al., 2015). Within Freesurfer v6.0, the segmentation tool generates an automated segmentation of the hippocampal subfields based on a statistical atlas built on ultra-high resolution (~1 mm isotropic) ex vivo MRI data. For the purposes of this study, cortical reconstruction and volumetric segmentation have already been performed with FreeSurfer (Fischl, 2012) v6.0 image analysis suite on the ADNI3 dataset, resulting in volumetric estimations of each subregion. Briefly, a multiatlas label fusion technique produces a fully automated segmentation of the hippocampal subfields along the entire length of the hippocampal formation. The automated process has been previously described in the literature (Wisse et al., 2016). For the purposes of this Aim, the following subfields were extracted for analysis: left and right CA1, left and right CA2, left and right CA3, and total ICV. Following the outlined guidelines, only segmented images with Quality Assurance (QA) scores ≥ 2 were used.

3.2.4 Statistical Analyses

Statistical analysis was performed in SPSS 28.0.0.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

3.2.5 Statistical Model

To determine whether the CA1 subfield volumes were related to the presence of delusions and if that relationship was moderated by the APOE ε4 allele, a repeated measure general linear model (GLM) was performed with the CA1, CA2, and CA3 subfields as within-subjects factors, The same models from Aim I were applied to the ADNI3 dataset and those results are listed in the Supplemental Material. APOE ε4 allele status and delusion presence as between-subjects factors, and with age, sex, and site as covariates. The conservative Bonferroni correction was employed for multiple testing (*p* values had to exceed .05/ (number of hippocampus subfields*number of

between-subjects factors) = 0.01. The relationship between MMSE scores, APOE status, and CA1 volume was examined using a repeated measures general linear model (GLM). The model included the CA1, CA2, and CA3 hippocampal subfields as within-subjects variables. APOE ε4 allele status and MMSE scores were included as between-subjects variables. Intracranial volume (ICV), age, sex, and site were included as covariates.

3.3 Results

Examining mean differences using analysis of variance (ANOVA), the left and right CA1 subfield volumes were compared across the APOE ε4 allele distribution and there were no significant difference between each allele status (left: $F = 0.252$, $p = .778$; right: $F = 1.096$, $p = .339$). Examining mean differences using *t*-tests, nonsignificant differences were found between both the left and right CA1 subfield volumes of those presenting with delusions (left: M = 968.86, SD = 247.88; right: M = 962.13, SD = 197.03) and those presenting without delusions (left: M = 945.84, SD = 251.51; right: M = 938.16, SD = 226.52; left: $p = .388$; right: $p = .370$). However, there was a significant difference in total ICV between individuals with delusions and individuals without delusions ($t = 3.027$, $p = .003$).

Delusions. A repeated measures GLM showed that the left CA1 volumes were not differently affected by either APOE ε4 allele status ($F(2) = 0.458$, $p = .634$) nor the presence of delusions ($F(1) = 1.511$, $p = .223$) when compared to the CA2 and CA3 subfield volumes. The right CA1 volumes were also not differently affected by either APOE ε4 allele status ($F(2) = 0.149$, $p = .862$) nor the presence of delusions ($F(1) = 0.001$, $p = .974$) when compared to the CA2 and CA3 subfield volumes. See Table 11 and Figures 9 and 10 for more details on the interactions.

Table 11. Repeated Measures ANOVA Results Comparing Delusions across CA Subfields.

	F	MS	df	*p*	Partial η squared
Left CA1					
Intercept	1.724	29064.642	1	.193	.022
ICV	25.171	424294.160	1	3.00E-6*	.244
Age	0.014	231.770	1	.907	.000
Sex	0.886	14941.410	1	.349	.011
Site	0.242	4081.404	1	.624	.003
Delusions	1.511	25471.064	1	.223	.019
APOE ε4 allele	0.458	7715.824	2	.634	.014
Delusions × APOE ε4 allele	0.559	9417.608	2	.574	.014
Right CA1					
Intercept	0.103	1564.216	1	.749	.001
ICV	16.483	249470.068	1	1.17E-4*	.176
Age	0.025	384.008	1	.874	.000
Sex	4.076	61690.011	1	.047	.050
Site	0.186	2822.329	1	.667	.002
Delusions	0.559	8467.409	1	.457	.007
APOE ε4 allele	0.455	9555.591	2	.636	.012
Delusions × APOE ε4 allele	0.450	6806.682	2	.639	.012

*Bonferroni corrected $p < .01$; df: degrees of freedom. ICV: intracranial volume (mm^3); Mauchly's test of sphericity ($p < .001$) adjusted df for averages tests of significance. Sex coded: Females = 2, Males = 1. Neither set of tests (left or right) passed significance.

Figure 10. Interaction of Delusions and APOE ε4 allele on Left CA1 volume (mm^3).

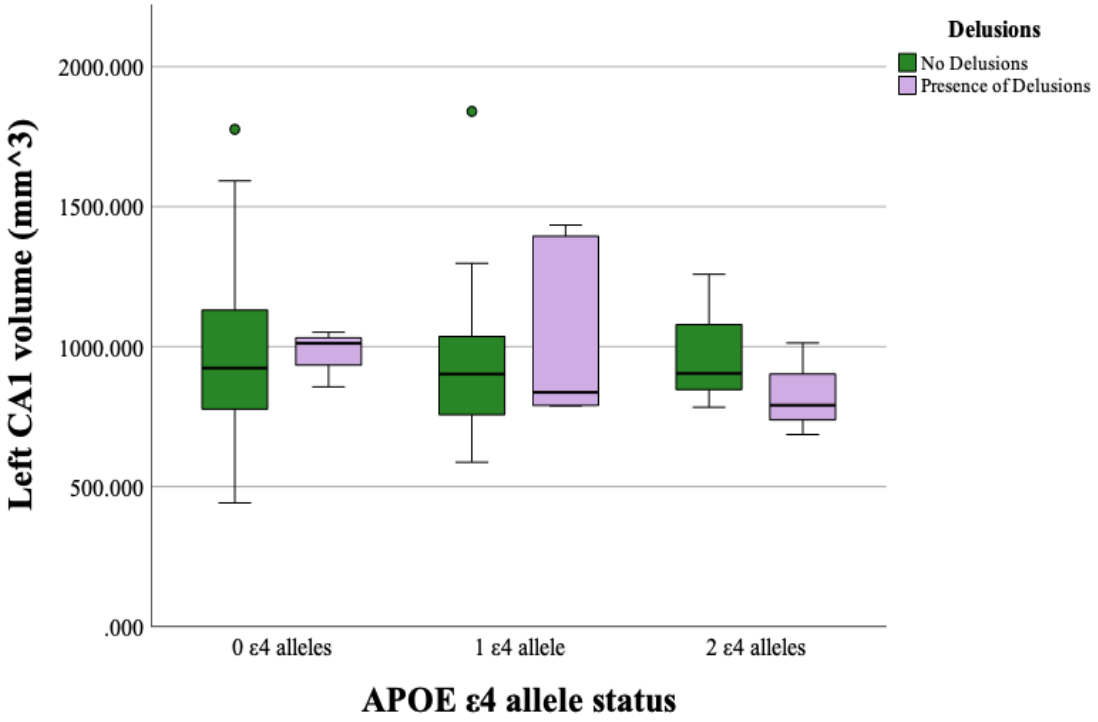


Fig 10. Results showed there was no significant interaction between APOE alleles and left CA1 volumes between individuals with delusions and individuals without delusions.

Figure 11. Interaction of Delusions and APOE ε4 allele on Right CA1 volume (mm^3).

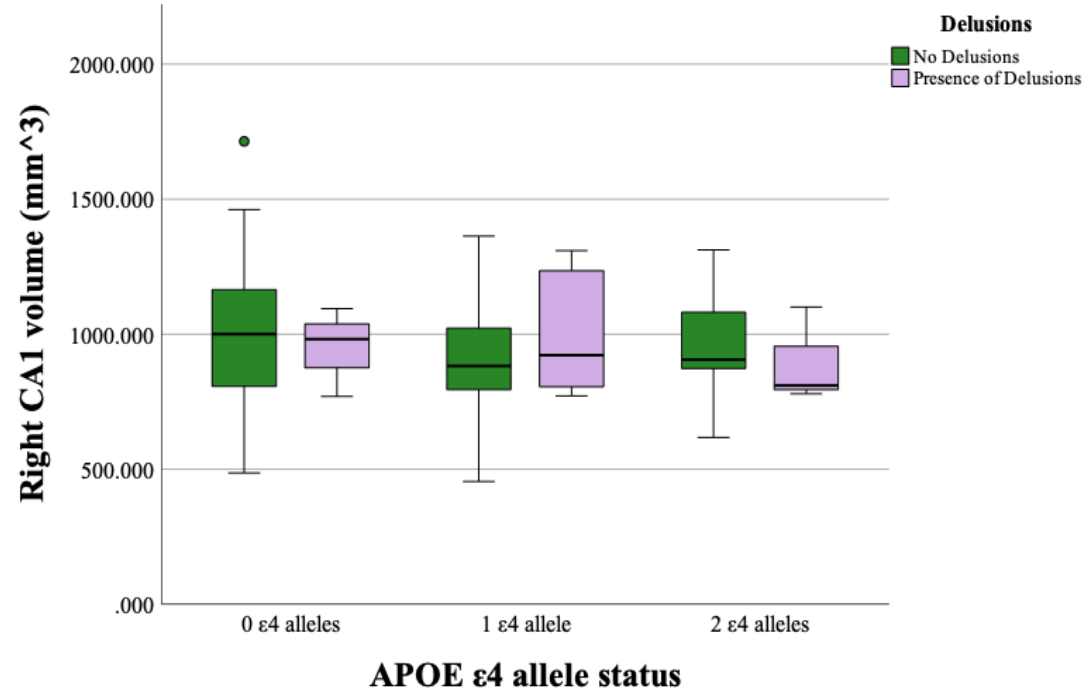


Fig 11. Results showed there was no significant interaction between APOE alleles and right CA1 volumes between individuals with delusions and individuals without delusions.

Independent samples *t*-tests showed a significant difference between the two groups (t = 2.641, p = .005) on MMSE scores. Individuals with delusions had an average MMSE score of 17.33 (SD = 6.63) and individuals without delusions had an average MMSE score of 22.12 (SD = 4.81). One-way ANOVA found no significant different across the APOE ε4 allele status and MMSE scores ($F(2) = 0.254$, p = .776). Pearson's correlations showed no significant relationship between MMSE scores and left CA1 subfield volumes (r = .198, p = .105) or between MMSE scores and right CA1 subfield volumes (r = .220, p = .074). There was also no significant correlation between MMSE scores and education attainment (r = -.044, p = .725). MMSE scores were significantly correlated with ICV volumes (r = .295, p = .015) and therefore, ICV was added to the repeated measures GLMs.

MMSE. A repeated measures GLM found that left CA1 volumes were not differently affected by either APOE ε4 allele status ($F(2) = 0.790$, p = .463) nor total MMSE score ($F(17) = 0.697$, p = .781) when compared to the CA2 and CA3 subfield volumes. The right CA1 volumes were also not differently affected by either APOE ε4 allele status ($F(2) = 1.171$, p = .324) nor by the MMSE scores ($F(17) = 0.906$, p = .574) when compared to the CA2 and CA3 subfield volumes. See Table 12 and Figures 12 and 13 for more details on the interactions. APOE ε4 allele status was also recoded as a binary factor and the repeated measures GLMs were analyzed with binary ε4 allele presence but the results did not differ significantly.

Table 12. Repeated Measures ANOVA Results Comparing MMSE across CA Subfields.

	F	MS	df	*p*	Partial η squared
Left CA1					
Intercept	0.842	17146.141	1	.366	.028
ICV	9.436	192136.472	1	.005*	.245

Age	0.019	392.935	1	.890	.001
Sex	2.349	47827.210	1	.136	.075
Site	0.037	747.014	1	.849	.001
MMSE	0.697	14191.815	17	.781	.290
APOE ε4 allele	0.790	16080.748	2	.463	.052
MMSE × APOE ε4 allele	0.481	9793.391	14	.925	.188
Right CA1					
Intercept	0.901	15865.248	1	.350	.030
ICV	2.665	46917.970	1	.113	.084
Age	0.011	195.845	1	.917	.000
Sex	2.283	40199.425	1	.142	.073
Site	0.665	11708.866	1	.421	.022
MMSE	0.906	15955.515	17	.574	.347
APOE ε4 allele	1.171	20622.021	2	.324	.075
MMSE × APOE ε4 allele	0.382	6726.323	14	.970	.156

*Bonferroni corrected $p < .01$; df: degrees of freedom. ICV: intracranial volume (mm^3); Mauchly's test of sphericity ($p < .001$) adjusted df for averages tests of significance. Sex coded: Females = 2, Males = 1.

Figure 12. Left CA1 volume (mm^3) across MMSE Scores distribution.

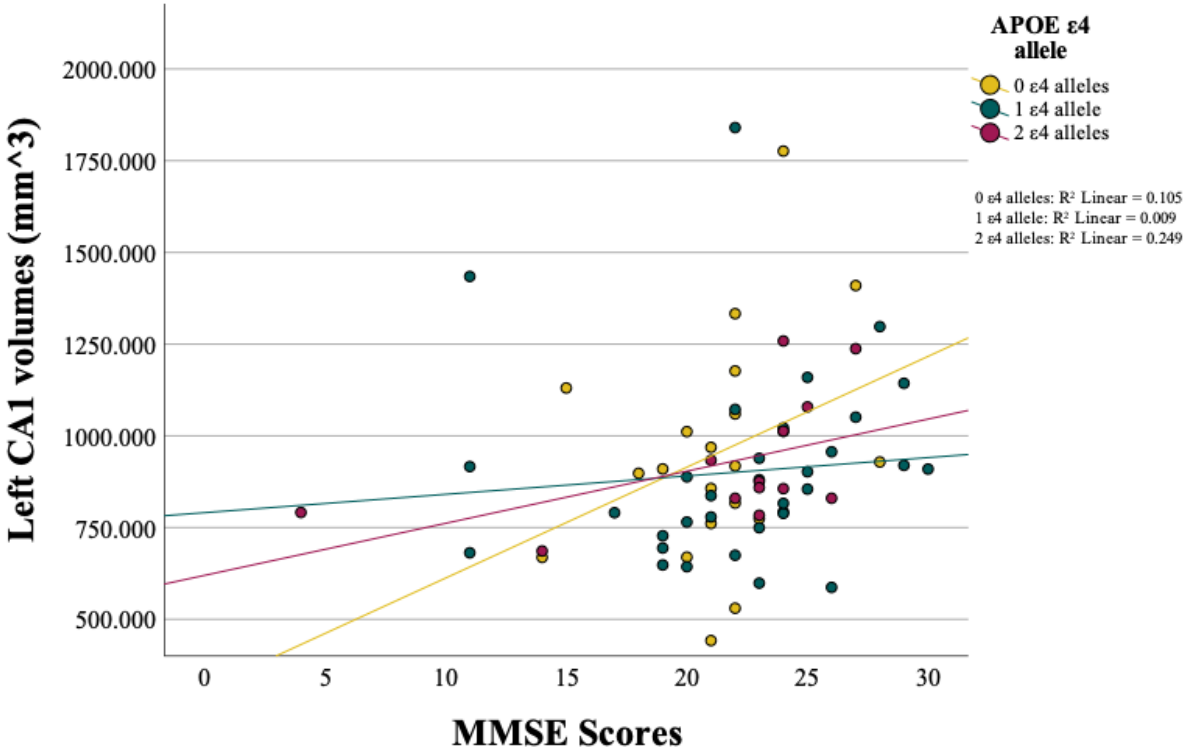


Fig 12. Results showed that the left CA1 volumes were not significantly associated with MMSE scores and that relationship was not significantly moderated by APOE ε4 allele presence.

Figure 13. Right CA1 volume (mm^3) across MMSE Scores distribution.

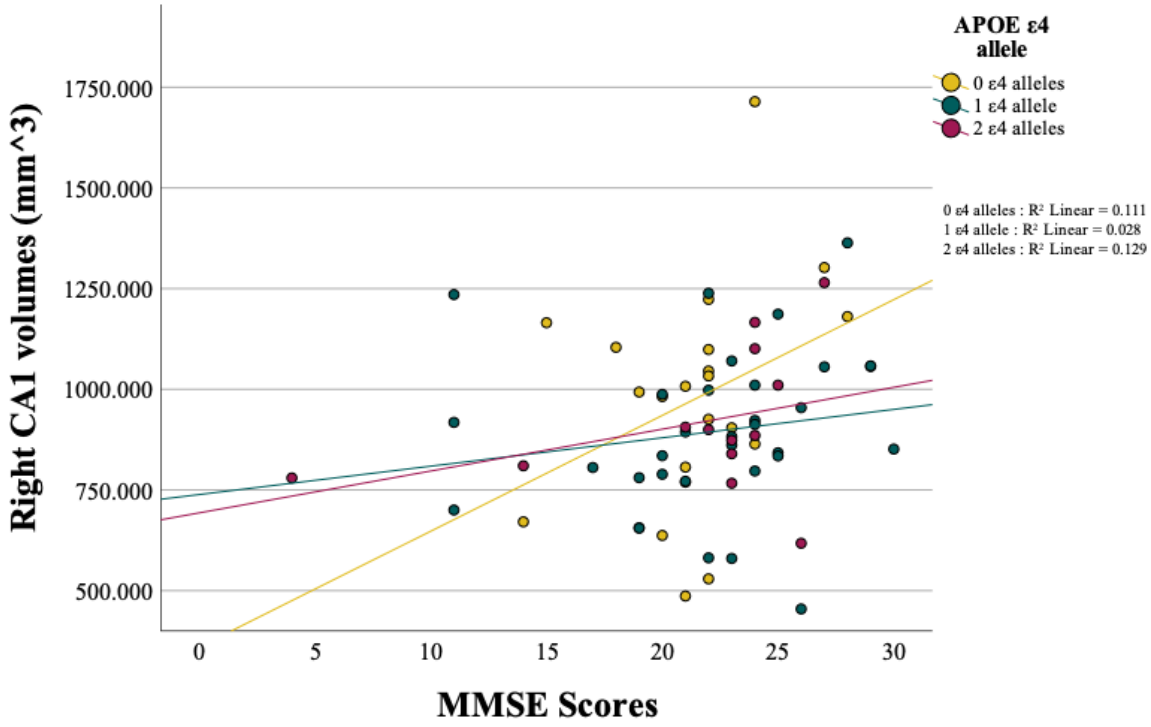


Fig 13. Results showed that the right CA1 volumes were not significantly associated with MMSE scores and that relationship was also not significantly moderated by APOE ε4 allele presence.

DISCUSSION

This study is one of the first to examine the specific symptom phenotype of delusions in Alzheimer's disease (AD) and its relationship to the hippocampal CA1 subfield and genotypic presentations. We expected a moderation of the relationship between CA1 volumes and presence of delusions and MMSE scores based on the APOE ε4 allele status. We acknowledge that the APOE ε4 allele status would not *cause* CA1 volume atrophy as cortical atrophy is observed in all individuals regardless of APOE ε4 allele status. However, we hypothesized that the APOE ε4 allele would moderate the relationship between CA1 atrophy and presence of delusions (as measured by the NPI-Q) such that the more APOE ε4 alleles an individual had, the more likely they would be to present with delusions regardless of CA1 volume. In the combined dataset (ADNI and OASIS) our results showed that there was no significant difference between individuals with delusions and individuals without delusions in any of the tested demographic information (age or sex) or in the distribution of APOE ε4 alleles, MMSE scores, or level of education.

These results indicate support for a possible neural aspect that is relating to, explaining, or causing the presence of delusions as our results show that the delusions are not explained by differences in cognitive impairment, diagnosis, age, or genetic presentation. From these results, we maintain our hypothesis that the cognitive status of AD (as measured by the MMSE) and delusions are two distinct clinical phenotypes relating to AD therefore, delusions are not an outcome or symptom of Alzheimer's disease and may have a unique neural component.

In Aim I, results show that individuals with delusions had significantly smaller right hippocampal volumes and smaller right CA1 subfield volumes when compared to individuals without delusions. Our results also found that the presence of delusions was not significantly related to the number of APOE ε4 alleles. The logistic regression model with age, sex, site, and

whole hippocampal volume also found no significant interaction between APOE ε4 alleles and either the left or right CA1 volumes in individuals with delusions. More specifically, the right CA1 subfield volume was smaller in individuals with delusions, but that association was not related to APOE ε4 alleles nor did that association survive multiple test correction.

In Aim I, individuals with delusions did not present with significantly different MMSE scores compared to individuals without delusions. MMSE score were significantly correlated with the left CA1 volume and both the left and right whole hippocampal volumes. There was a significant effect of APOE ε4 alleles on MMSE scores, which was to be expected given APOE ε4 allele's increased risk for AD severity (Belloy et al., 2019; Corder et al., 1993). However, in a similar manner as delusions, the MMSE association with hippocampal volumes and APOE ε4 alleles did not survive once age, sex, and site were accounted for in the model. There was no significant interaction between APOE ε4 alleles and CA1 volumes (right or left) with either the presence of delusions or the MMSE scores.

In Aim II, we used high resolution T2 images from a subset of the ADNI dataset to further expand upon the findings of Aim I. The goal of Aim II was to examine possible CA1 volumetric differences in the individuals with delusions and determine if the differences in the CA1 were unique to that subfield by comparing it to the other hippocampal subfields (CA2 and CA3). The high resolution of T2 MRI images lends itself to a more accurate segmentation of the hippocampus along subfield lines, allowing for a more precise analysis of CA1 volume as a biological correlate of the APOE ε4 pleiotropic effect. The improvement in segmentation accuracy is observable by the increase in average CA1 volumes when comparing across Aim I and Aim II.

There was a significant difference in the total intracranial volume between individuals with delusions and individuals without delusions. However, we did not observe any significant differences in the CA subfields of the hippocampus in relation to the APOE ε4 alleles on either the presence of delusions or the MMSE scores. The number of APOE ε4 alleles did appear to influence the relationship between CA1 volumes and MMSE as observed in Figures 11 and 12, with the positive relationship between both the left and right CA1 volumes and MMSE decreasing with increased number of APOE ε4 alleles. However, neither of those associations reached significance. One noted limitation that will discussed further is the resulting small sample size of the ADNI3 dataset for Aim II.

Overall, these results do not support the original hypothesis that there is a moderating relationship of the APOE ε4 allele between the CA1 subfield volumes and delusions. In addition to the limitations of the study design, we hypothesize two explanations for the lack of significant reductions within the CA1 subfields observed in individuals with delusions. As noted in Aim II, the hippocampal segmentation resulting from ~1mm^3 T1 images may not be a valid measure of the true volumes of the individual hippocampal subfields (Wisse et al., 2021). Our results show support for this claim as the average CA1 volume increased substantially from the T1 images in Aim I to the T2 images in Aim II. Furthermore, in comparing the small subset of individuals who were included in both sets of analyses, there were noted increases in CA1 volumes even within the same person. Therefore, we conclude that our results from Aim I did not show a moderating relationship of the APOE ε4 allele on CA1 volumes in individuals with delusions partially because of the small subfield segmentations. However, there was still no significant association identified in Aim II. Therefore, lack of significant findings cannot be solely explained by the hippocampal segmentation.

Our second explanation relates to the sample's rate of APOE ε4 allele presentations. In this study, 73.53% of individuals with delusions had at least one APOE ε4 allele, whereas 61.42% of individuals without delusions had at least one APOE ε4 allele compared to 13.7% of individuals in the general population. Although the APOE ε4 allele is related to an increased risk for Alzheimer's disease and especially late-onset Alzheimer's disease (Belloy et al., 2019; Corder et al., 1993), our results show that possession of an APOE ε4 allele was not related to an increased risk for delusions. In both set of results, there was no significant association between APOE ε4 allele possession and the presence of delusions. As mentioned above, a trend, but non-significant, of the APOE ε4 allele was also observed in the relationship between MMSE scores and CA1 volumes from Aim II. In other words, possession of the APOE ε4 allele resulted in worse MMSE scores even with large CA1 volumes when compared to individuals without APOE ε4 alleles. Given these findings, we argue that the APOE ε4 allele may not be the cause of effect in the relationship between delusions and the CA1. Although the previous literature points to a potential relationship between APOE ε4 alleles and delusions, it is possible that the APOE ε4 allele is related to more severe presentations as well as late-onset AD and delusions tend to present in later stages of the disease. Previous GWAS studies have reported a small (but significant) association between the APOE ε4 allele and psychosis in large studies (N > 12,000) but there are also some inconsistent findings in smaller sample sizes (Creese et al., 2019; DeMichele-Sweet et al., 2018, 2021; Shah et al., 2017). Therefore, the APOE ε4 allele and delusions may be observed in the same AD presentations but are not directly related. To examine this limitation, we removed APOE ε4 alleles and its interaction with the CA1 subfields from the models in Aim I, but there were no notable differences to the results. We conclude that we did not find support for possession of the APOE

ε4 allele indirectly influencing the presentation of delusions because of the small sample size and the weighted percentage of APOE ε4 allele possession already in this AD sample.

Examination of the entire symptom profile of individuals presenting with delusions within AD may inform the pathophysiology better than examination of the symptom as a single entity. Previous studies have identified that individuals with depression and AD had an increased rate of delusions compared to individuals without depression (Bassiony et al., 2002). Delusions in AD were also significantly associated with agitation and physical aggression, in addition to depression (Mizrahi et al., 2006). There are also high rates of delusions and hallucinations presenting together in AD and other dementias (Dave et al., 2020; Ffytche et al., 2017; Fischer & Sweet, 2016; Murray et al., 2014; Sakai et al., 2019). These symptoms may simply be co-occurring within the complexities if Alzheimer's disease, may be secondary to the cognitive deficits and other functional difficulties that arise from Alzheimer's disease, or may relate to the same pathophysiology and therefore, should be studied as an whole symptom presentation to fully understand the genetic and neural underpinnings of delusions in AD.

The lack of significant structural findings in this study may indicate that a more accurate description of this relationship is the *connectivity* of the CA1 subfield within the cortex. As previously mentioned, the CA1 subfield has been implicated in novelty detection, information input comparison, autobiographical memory, and autonoetic consciousness. Previous literature examining the CA1 have found associations with the CA1 and psychosis that were not only volumetric. Pyramidal cell death in the CA1 was originally hypothesized as a primary cause of paranoid delusions (Krieckhaus et al., 1992). Lower neuron counts in the CA1 were related to misidentification delusions (Förstl et al., 1994) and focal brain lesions were identified in the CA1 regions of individuals who presented with Capgras delusion (Feinberg & Keenan, 2005). In

addition, functional connectivity found CA1 alterations were related to overall positive symptoms in schizophrenia and other psychiatric disorders (Schobel et al., 2009). Therefore, we conclude that a potential CA1 subfield and delusion relationship should be further examined in connectivity studies.

Another approach to examining the CA1 and delusion relationship may be longitudinal studies. Using the ADNI dataset, researchers found greater rates of volumetric atrophy in the left hippocampus and bilaterally in the parahippocampal gyri in individuals with delusions compared to individuals who did not develop delusions (Manca et al., 2022). Atrophy was observed in other regions along the dopaminergic pathway, indicating support for the CA1 being a small part of a larger network relating to delusions (Manca et al., 2022). Examination of the findings showed insignificant differences across groups in the final time point (as we did in this current study) but the change over time between the two groups was significant. Therefore, our cross-sectional approach may have limited the potential for observing differences in the CA1 volumes of individuals with and without delusions.

Although our findings do not directly support a relationship between CA1 subfields, APOE ε4 allele and delusions, we did find that individuals with delusions present with significantly smaller right CA1 volumes compared to individuals without delusions. Therefore, there is still support for the CA1 playing a role in the presence of delusions. The CA1 subfield relates and has connections to the sensorimotor cortex, amygdala, orbitofrontal cortex, medial and lateral temporal poles, and the nucleus accumbens (Ezama et al., 2021). These regions are responsible for processing of discriminatory sensory information, which may indicate that a dysfunction in these regions could relate to a lack of discrimination in incoming sensory information and that may explain the development and maintenance of delusions. Furthermore, reduced activation was

observed in the spatiotemporal/visual attention region in individuals with schizophrenia and delusions in the face of weak evidence when compared to individuals without delusions. These results imply that individuals with delusions do not *scrutinize* weak evidence to the same extent as individuals without delusions (Fouladirad et al., 2022). However, the directionality of the connectivity in delusions is still unclear. In AD individuals with delusions, weaker connectivity was observed in the default mode network (DMN) and the superior temporal gyrus, left interior orbitofrontal and right medial orbitofrontal (Qian, Fischer, et al., 2019). On the other hand, increased connectivity between the hippocampus and the amygdala was observed in individuals experiencing paranoia, a common theme of delusion presentation (Walther et al., 2022). These results indicate that delusions may be a product of dysfunction of connected networks in the brain, specifically the hippocampus, and not solely a loss of function associated with a loss of gray matter volume. The question remains as to what causes the dysfunction in these networks if it is not specifically a greater loss of volume.

4.1 Limitations

There are a few limitations of this study. To begin, both Aims were severely limited in sample sizes. Given the quality of the T1 MRI and T2 MRI images as well as the number of participants with completed assessments, the sample sizes were smaller than originally proposed. Power analyses were completed prior to study to confirm that the sample sizes would yield sufficient effect sizes. With moderate effect size (0.20 for F test), α level at 0.025, the minimal total sample size to achieve power over 90% (assuming equal sample size in each group) is 108 (54 for each group) (Faul et al., 2007). In Aim I, our delusion sample size (N = 73) was slightly above this power requirement. In Aim II, our delusion sample size was severely under this power requirement (N = 11). Although we tried to overcome the limitations of a small sample by

examining one predefined region of interest (the CA1 subfield), a moderate effect size may have been overly optimistic for either Aim. If we set effect size to be small, effect size = 0.2, α level at 0.025, and power = 0.90, the minimal total sample size would be 450 (225 for each group), in which case all our analyses are underpowered.

Second, the use of the MMSE may not be an accurate representation of general cognitive status. The MMSE is a useful symptom tool for individuals with normal cognitive functioning or mild and moderate cognitive decline. In addition to the previously mentioned limitations of the MMSE observed across education levels, gender, and race/ethnicity, it has also been noted that high scores can be achieved on the MMSE even if the individuals have significant cognitive deficits and this is especially noted in individuals with higher levels of baseline education (e.g., completed college degrees and above). We examined education levels and there was a significant correlation between MMSE and education (see Supplemental Material) but there were no noted differences in education between individuals with delusions and individuals without delusions or correlations between education and site, age, or APOE ε4 allele distribution.

Third, the examination of delusions within the context of AD can be challenging to accurately assess. Furthermore, the binary categorization of this complex symptom has limitations. Without examining the nature and type of the delusion, we were assuming that all delusion presentations would have the same association with the APOE ε4 allele and CA1 subfield volume. However, there are multiple delusion types that may support the notion of different networks relating to different presentations. Delusion type falls broadly into twelve different categories with some discrepancies: persecutory, jealousy, grandiosity, religious, delusion of reference, erotomania, guilt, somatic, and passive delusions such as, thought withdrawal, thought insertion, thought broadcasting, and the delusion of being controlled. There

are additional categories of delusions that are more specific, such as Capgras delusion (believing family members are replaced by an identical imposter) and Othello's syndrome (delusional jealousy about family members) that have been observed across disorders (Moro et al., 2013).

Most notably, individuals with Alzheimer's disease tend to report delusions of misidentification and persecutory delusions. Different types of delusions may indicate different underlying psychopathological constructs (e.g., deficits in self-monitoring versus deficits in source monitoring). Future studies should examine the full spectrum of the delusion presentation to determine if any one presentation relates more to volumetric changes in the hippocampus and specifically the CA1 subfield.

4.3 Conclusions

In this study, we examined the relationship between APOE ε4 allele status, CA1 subfield volumes, and the presence of delusions in a combined Alzheimer's disease dataset. We also sought to examine the specificity of relationship between delusions and the CA1 subfield as it related to the other hippocampal subfields. We did not find a significant relationship between the CA1 subfields, APOE ε4 alleles, and the presence of delusions. Individuals with delusions had significantly smaller right CA1 volumes and APOE ε4 allele did moderate a relationship between left CA1 volumes and MMSE scores but no other findings were significant. We caution that these findings do not completely dissuade a relationship between the CA1 subfield and delusions as no other notable differences were found. Further comparisons were unable to find any significant group differences in any participant demographic information. Therefore, we conclude that there is still a possibility of an association between the CA1 subfield and delusions, but future research is needed to examine functional connectivity aspects of the CA1 and more

broadly, the hippocampus, and how this region may be relating to the presence of delusions in AD.

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Supplemental Material

Supplemental Table 1. Binary APOE ε4: Cox and Snell R2 and Total Model χ2 Change.

	Cox and Snell R^2	Block χ^2	*p*	Total model χ^2	*p*
Left CA1					
Age, Sex, Site	.165	69.59	.075	69.59	.075
APOE ε4 allele (binary)	.169	2.17	.141	71.75	.064
Left CA1 & Whole hippocampus	.170	0.161	.923	71.91	.088
Left CA1 × APOE ε4 allele (binary)	.170	.001	.978	71.91	.104
Right CA1					
Age, Sex, Site	.165	69.59	.075	69.59	.075
APOE ε4 allele (binary)	.169	2.17	.141	71.75	.064
Right CA1 & Whole hippocampus	.173	1.95	.377	73.70	.068
Right CA1 × APOE ε4 allele (binary)	.180	3.22	.073	76.93	.049

In addition to the analyses described in the main manuscript, we also examined educational attainment across multiple variables. There was no significant difference across APOE alleles and educational attainment ($F(2)=0.433$, $p = .649$). Although individuals with delusions had less average education scores, there was no significant difference in education between individuals with delusions (M = 14.97, SD = 3.023) and individuals without delusions (M = 15.19, SD= 2.93; $t = 0.571$, $p = .284$). There was a significant correlation between MMSE and education ($r = .096$, $p = .043$).

Supplemental Table 2. Linear Regression Block Design Results for Left and Right CA1 Subfields on MMSE Scores.

	Adjusted R^2	F	Mean Square	*p*
Left CA1 head				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele	.005	1.432	36.848	.223
Left CA1 head & whole hippocampus	.018	2.146	54.453	.048
Left CA1 head × APOE ε4 allele	.015	1.837	46.738	.079
Left CA1 body				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele	.005	1.432	36.848	.223
Left CA1 body & whole hippocampus	.017	2.062	52.395	.057
Left CA1 body × APOE ε4 allele	.015	1.796	45.739	.087
Right CA1 head				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele	.005	1.432	36.848	.223
Right CA1 head & whole hippocampus	.009	1.575	40.343	.153
Right CA1 head × APOE ε4 allele	.008	1.448	37.103	.185
Right CA1 body				
Age, Sex, Site	.005	1.601	41.174	.189
APOE ε4 allele	.005	1.432	36.848	.223
Right CA1 body & whole hippocampus	.009	1.572	40.258	.154
Right CA1 body × APOE ε4 allele	.007	1.358	34.854	.222

For Aim II, the ADNI3 T2 images were used in the same models as Aim I to compare if the accuracy from the increased resolution would show an effect. See Supplemental Tables 3 and 4 for more details.

Supplemental Table 3. Block Design Logistic Regression with ADNI3 T2 Images.

	Cox and Snell R^2	Block χ^2	*p*	Total model χ^2	*p*
Left CA1					
Age, Sex, Site	.293	30.502	.861	30.502	.861

APOE ε4 allele	.316	2.955	.086	33.457	.793
Left CA1 & ICV	.341	3.256	.196	36.713	.739
Left CA1 × APOE ε4 allele	.342	0.070	.791	36.783	.771
Right CA1					
Age, Sex, Site	.293	30.502	.861	30.502	.861
APOE ε4 allele	.316	2.955	.086	33.457	.793
Right CA1 & ICV	.335	2.475	.290	35.932	.769
Right CA1 × APOE ε4 allele	.336	.153	.696	36.085	.796

*Bonferroni corrected $p < .05$. No results passed significance.

Supplemental Table 4. Block Design Linear Regression with ADNI3 T2 Images.

	Adjusted R^2	**F**	**Mean Square**	***p***
Left CA1				
Age, Sex, Site	.047	2.082	42.170	.111
APOE ε4 allele	.032	1.543	31.736	.201
Left CA1 & ICV	.050	1.580	31.890	.169
Left CA1 × APOE ε4 allele	.049	1.490	30.091	.189
Right CA1				
Age, Sex, Site	.047	2.082	42.170	.111
APOE ε4 allele	.032	1.543	31.736	.201
Right CA1 & ICV	.072	1.848	36.456	.105
Right CA1 × APOE ε4 allele	.070	1.710	33.790	.124

*Bonferroni corrected $p < .05$. No results passed significance.