2022-08-10

The Relationship Between Thalamic Morphology and Behavioral Features in Amnestic and Aphasic Variants of Alzheimer's Disease

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A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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ABSTRACT

The Relationship Between Thalamic Morphology and Behavioral Features in Amnestic and Aphasic Variants of Alzheimer's Disease

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Background: The presence of AD pathology can result in diverse behavioral phenotypes, including the typical amnestic variant characterized by memory deficits, and an atypical aphasic variant characterized by language deficits. Previous research has identified unique cortical atrophy patterns in each phenotype, though less focus has been drawn to subcortical involvement. The current study sought to dissociate these behavioral phenotypes by characterizing their thalamic volume and shape features using high-dimensional brain mapping procedures. Relationships between brain metrics and specific language and memory deficits were also investigated in aphasic AD and amnestic AD, respectively.

Method: Thalamic integrity was examined in aphasic AD (n = 25), amnestic AD (n = 21), and healthy control participants (n = 44). Age and supratentorial volume (STV) were used as covariates in all analyses. MR scans were acquired using high-resolution T1-weighted MPRAGE volumes following the ADNI protocol. Thalamic shape features were estimated using Large Deformation Diffeomorphic Metric Mapping. General linear models compared differences in thalamic shape between groups. Pearson correlation coefficients characterized relationships between thalamic nuclei (pulvinar, anterior, and mediodorsal) and language and memory performance in aphasic AD and amnestic AD, respectively.

Results: After controlling for age and STV, thalamic volume did not differ between groups [$F(2,85) = 2.55$, $p = 08$]. However, AD phenotypes exhibited bilateral inward shape deformation in dorsal and ventral regions extending in an anterior to posterior fashion [left: $F(20, 154) = 2.61$, $p < .001$; right: $F(20,154) = 2.26$, $p < .01$]. Amnestic AD demonstrated right ventrolateral localized volume loss relative to aphasic AD. Pearson models revealed lower confrontation naming was correlated with localized volume loss of bilateral pulvinar (left: $r = .59$, $p < .01$; right: $r = .55$, $p < .01$), and bilateral anterior (left: $r = .50$, $p = .01$; right: $r = .49$, $p = .01$) thalamic nuclei for aphasic AD; lower delayed recall was significantly correlated with localized volume loss in left anterior ($r = .46$, $p = .04$) thalamic nuclei in amnestic AD.

Conclusions: In the absence of volumetric differences, shape measures captured distinct patterns of localized volume loss in aphasic AD and amnestic AD behavioral phenotypes relative to control participants. Comparisons of AD variants demonstrated inward deformation in amnestic AD, particularly in right ventrolateral regions. Thalamic changes appear to be implicated in AD pathology, with relationships to the expected cognitive impairments, although thalamic atrophy patterns are unable to fully dissociate behavioral phenotypes.

Keywords: Alzheimer's disease, primary progressive aphasia, shape analysis

ACKNOWLEDGMENTS

I am grateful to all that made this possible. I would like to thank Dr. Derin Cobia, for his thoughtfulness, direction, and mentorship throughout the years. I am incredibly appreciative of his never-ending support. My sincere thanks goes to my committee for their flexibility, support, and insights. I would like to thank the team at Northwestern University Feinberg School of Medicine for allowing me the opportunity to be involved in this research.

Finally, I would like to thank my husband, Andrew, for sticking by my side for all of our cross-country moves, the late-night presentation run-throughs, and the venting sessions when I needed them most. He has been an incredible support and I could not have done any of this without him. I am grateful for my parents for being the greatest role models and always believing in and encouraging me. And a final thanks to my son, Carter, for making the last part of this journey a bit unexpected and that much more worth it.

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Need for the Study

Alzheimer's disease (AD) is a neurodegenerative disease and the most common cause of dementia. In 2021, it is estimated that 6.2 million Americans are living with dementia due to AD, affecting 11.3 percent of people aged 65 and older (Alzheimer's Association, 2022). Incidence estimates vary with recent estimates in people ages 65-74 at 0.4 percent up to 7.6 percent in people aged 85 and older, numbers that are expected to increase as the general population age increases (Alzheimer's Association, 2022). Long-term care of individuals with AD means increased caregiver and financial stressors. Of family caregivers, approximately 30 percent are also over the age of 65 (Alzheimer's Association, 2022). In addition to caregiver stress, financial stress is evident as total costs for all individuals with Alzheimer's or other dementias in the United States is estimated at $355 billion (Alzheimer's Association, 2022). AD is the sixth-leading cause of death in the United States and the fifth-leading cause of death in individuals over the age of 65, though this may reflect an underestimation of official deaths (Alzheimer's Association, 2022). The impact of AD is profound and efforts to improve strategies aimed at the diagnosis, management, and treatment of AD is increasingly important.

Problem to be Addressed

AD pathology is characterized by neurofibrillary tangles, beta-amyloid plaques, and cerebral atrophy. Extensive research has focused on understanding neuroanatomical changes that result from AD pathology and the subsequent impact on cognitive functioning (Guillozet et al., 2003; Mielke et al., 2012; Bakkour et al., 2013). However, the presence of AD pathology does not necessarily result in a single identical clinical phenotype across individuals. For example,

AD pathology is present in 10-60% of cognitively intact middle aged to older adults that may or may not experience future cognitive declines (Jansen et al., 2015). AD pathology is also the most prevalent cause of dementia, referred to as "Dementia of the Alzheimer's type" (DAT), accounting for at least 60-70% of individuals diagnosed with dementia (Mielke et al., 2014). Age of disease onset in individuals with DAT is 65 years or older with a slightly higher prevalence in females (Rogalski & Mesulam, 2009). Of these individuals, the typical clinical presentation is characterized by impairments in learning and memory (McKhann et al., 2011). Specifically, individuals with this type of amnestic variant of AD, present with a gradual onset and initial progressive decline in learning and recall of recently learned information accompanied by progressive deficits in other cognitive domains as the disease progresses, including executive dysfunctions, anomia, visuospatial deficits, and/or neuropsychiatric symptoms (McKhann et al., 2011). In contrast, some individuals present with atypical phenotypes of AD neuropathology including a non-amnestic syndrome characterized by language impairments (discussed further below). Given that AD pathology can result in distinct clinical phenotypes, it is important to elucidate the neuroanatomical differences underlying the different variants of AD. In other words, are there dissociating anatomical features between clinical phenotypes of AD considering the presence of similar underlying pathology?

Purpose of the Study

The purpose of the current study is to characterize thalamic integrity using volumetric and morphologic analyses in two known AD pathology clinical phenotypes – namely the aphasic and amnestic variants – and relate it to various aspects of their cognitive presentation.

Justification

The rationale for this approach is to leverage a dissociation model to characterize relationships between observable behaviors and underlying brain integrity. Previous work from our group demonstrated a unique pattern of thalamic deformation that related to confrontation naming performance in a well-characterized sample of individuals with aphasic AD. The current study will expand upon these findings by including an amnestic AD group to determine whether AD pathology differentially affects the thalamus in these groups and can potentially account for their unique clinical phenotypes. Overall, this study will clarify the role of the thalamus in various clinical AD phenotypes and its relationship with primary cognitive domains. It is anticipated that findings will influence strategies aimed at the diagnosis, management, and treatment of those with AD pathology.

Review of the Literature

Aphasic AD Definitions

Primary Progressive Aphasia (PPA) is a dementia syndrome characterized by initial dissolution of various language functions. Prevalence of PPA remains unknown, though recent estimates indicate a prevalence of 3.0/100,000 individuals (Bergeron et al., 2018). In contrast with amnestic AD, the onset of symptoms in PPA typically occurs before the age of 65, with a slightly higher prevalence recorded in males (Rogalski & Mesulam, 2009). According to Gorno-Tempini et al. (2011), a root diagnosis of PPA requires that language difficulties be the most prominent deficit at symptom onset and in the initial phases, with activities of daily living remaining intact in initial stages except for those that require the use of language. A differential diagnosis of PPA requires that aphasic features occur in the absence of stroke, tumor, or other neurological insult and that non-language related cognitive domains remain intact (i.e., non-

verbal memory, visuospatial functioning, etc.). Language functioning progressively worsens over time and remains the most impaired function throughout the course of the disease. Although other domains may be affected approximately two years after disease onset, language functions continue to decline faster than other cognitive domains (Sonty et al., 2003).

Underlying neuropathology of PPA reveals neuropathological agents consistent with frontotemporal lobar degeneration (FTLD) and AD. Approximately 30-40% of individuals with PPA have suspected AD pathology (Mesulam et al., 2008; Knibb et al., 2005; Rogalski & Mesulam, 2009), and notably PPA due to AD pathology is often referred to as the *aphasic variant of AD* (Rogalski et al., 2019). Specific risk factors for PPA remain unknown and most individuals diagnosed with PPA are sporadic cases, though a small number of individuals have genetic forms of the disease (Rogalski & Mesulam, 2009). In contrast, it is well established that the apolipoprotein ε (ApoE) gene is a risk factor for AD pathology in the amnestic variant of AD, though this gene has shown no relationship to the aphasic variant of AD (Rogalski et al., 2011c). In the search for susceptibility factors, there is some evidence to suggest a history of learning disability may indicate a greater likelihood for developing PPA in adulthood though further investigations into the replicability of this finding and the underlying mechanism are necessary (Rogalski et al., 2013).

Aphasic Variant - Language Profile

Regardless of underlying pathology, three PPA subtypes have been identified based on language profiles, clinical presentation, and neuroanatomical changes – these are referred to as: agrammatic (PPA-G), logopenic (PPA-L), and semantic (PPA-S) subtypes. A fourth "mixed" (PPA-M) subtype has been proposed for individuals with a clinical presentation that does not fit into the other diagnostic categories (Mesulam et al., 2012). The clinical presentation of the PPA-

S subtype differs significantly from the two non-semantic subtypes (PPA-L and PPA-G) as the key language deficits in individuals with non-semantic forms of PPA are characterized by semantic and phonemic paraphasias, impaired single word retrieval, effortful/halting speech, etc., whereas individuals with semantic PPA are characterized by impaired object naming and object knowledge, dyslexia/dysgraphia, and impaired single word comprehension (Gorno-Tempini et al., 2011). As mentioned previously, a portion of individuals with PPA demonstrate excessive burden of underlying AD pathology, with approximately 86% of people diagnosed with PPA-L and 20% of individuals diagnosed with PPA-G showing this burden as predicted by positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers (Bergeron et al., 2018). It is believed the neuropathological profile of the semantic PPA subtype is characterized by an absence of AD pathology (Alladi et al., 2007; Rohrer et al., 2012).

The following section refers to classification criteria set forth by Gorno-Tempini et al. (2011). A diagnosis of PPA-G requires the presence of at least one of the following symptoms: agrammatism in language production or effortful/halting speech with apraxia of speech. At least two associated features must be present including impaired comprehension of syntactically complex sentences, spared single-word comprehension, or spared object knowledge. Typically, the first observable symptom is effortful speech before obvious apraxia of speech is noted. Taken together, patients with PPA-G typically present with disrupted prosody and slowed rate of speech with marked errors in speed sounds (i.e., omissions, substitutions, mispronunciations, etc.). Comparatively, the rate of speech in individuals with PPA-G is approximately less than one-third that of healthy adults (Ash et al., 2019). The course of the disease is progressive until speech of any kind is minimal to absent (Ash et al., 2019).

A diagnosis of PPA-L requires the presence of both impaired single-word retrieval in spontaneous speech and naming, and impaired repetition. At least three associated features must be present including phonologic errors, spared single word comprehension and object knowledge, spared motor speech, and absence of agrammatism. Patients with PPA-L typically present with slow and halting speech characterized by word-finding pauses. It should be noted that patients with PPA-G also present with slow and halting speech which can be differentiated from PPA-L based on the characteristic agrammatic and sound errors in speech output as opposed to pauses for word-finding.

Confrontation Naming

One prominently impaired language function in non-semantic PPA subtypes (agrammatic and logopenic) is confrontation naming, defined as the ability to retrieve a single word in response to a stimulus (Gorno-Tempini et al., 2011). Confrontation naming can occur across any sensory modality but has mostly focused on the verbal naming of visually presented objects in both clinical and research contexts. Adequate object naming performance requires the integration of various levels of processing, meaning that naming deficits may result from errors in perceptual, semantic, and/or phonological processing. Specifically, the hypothesized stages involved in confrontation naming include 1) visual processing and recognition, 2) semantic processing, 3) selection of an abstract representation, and 4) execution of the output (Gleighgerrcht et al., 2015). It is suggested that individuals with non-semantic PPA typically demonstrate errors in the final two stages – selection of an abstract representation and execution of the output (Gleighgerrcht et al., 2015). Contrary to semantic processing, which involves the knowledge of what an object is (i.e., recognizing that a presented stimulus is a fruit), abstract representation refers to one's ability to retrieve the name of the object (i.e., recognizing that

"orange" represents the fruit). This action is also called lexical access, and failure to accurately retrieve the name of an object represents the "tip of the tongue" phenomenon often experienced in aphasic AD (Gleighgerrcht et al., 2015). Additionally, the pattern of halting speech and paraphasias in individuals with aphasic AD is consistent with difficulties at this level of processing as individuals will pause and/or use similar, though incorrect, words to replace those they cannot retrieve. It should be noted that differentiating between various levels of processing in confrontation naming tasks is difficult, and many studies focus on the accuracy of naming rather than the level of processing. That is, many studies may label a task as "semantic processing" even if it involves all stages of processing.

A study by Hurley et al. (2012) supported the idea of multiple confrontation naming processing stages by identifying two types of anomia in PPA where participants with non-semantic PPA exhibited difficulties with semantic retrieval, indicating some preservation of the link between an object and its lexical label, though the information could not be spontaneously retrieved. In contrast, semantic forms of PPA exhibited a complete disconnect between object and label, such that individuals could not recognize the correct specific words but could identify related generic words. Overall, there is support for the existence of naming deficits in individuals with non-semantic PPA/aphasic AD that are due to errors at the level of selection/retrieval of semantic representation.

The Neuropathology of Aphasic and Amnestic AD

Studies of neuropathological changes underlying AD pathology have largely focused on cortical atrophy patterns. Relative to cortical thinning observed in normal aging, there are regions of overlap noted in amnestic AD, including dorsolateral prefrontal and inferior parietal cortex (Bakkour et al., 2013). More importantly, unique areas of cortical atrophy specific to

amnestic AD include medial temporal cortical regions, namely the rostral ventromedial temporal lobe within entorhinal and perirhinal cortices, patterns which are evident early in the disease process (Bakkour et al., 2013). Relative to individuals with amnestic mild cognitive impairment (aMCI), AD subjects demonstrate increased cortical atrophy, as measured by cortical thickness, in bilateral temporal and frontal regions, with the largest difference between groups in the left lateral temporal area (Singh et al., 2006). In aphasic AD, extensive cortical atrophy has been observed across the entirety of the left hemisphere, most prominently in perisylvian areas that include temporal, frontal, and parietal lobes (Rogalski et al., 2011a; Gorno-Tempini et al., 2004). In summary, individuals with amnestic AD typically exhibit atrophy in bilateral anterior and ventral regions of the medial temporal lobes, whereas individuals with aphasic AD typically exhibit atrophy in left perisylvian areas (Gefen et al., 2012).

More recently, research has focused on directly comparing atrophy patterns between the clinical phenotypes of AD. Studies suggest differences may exist in the hemispheric distribution of lesions, specifically asymmetry of neurofibrillary tangles predominantly in the left hemisphere in aphasic AD subjects relative to a symmetrical distribution pattern in amnestic AD (Gefen et al., 2012). Furthermore, a higher neocortical-to-entorhinal ratio of neurofibrillary tangles was observed in aphasic AD subjects relative to subjects with amnestic AD, with an overall greater number of both tangles and plaques especially in neocortical areas in aphasic AD subjects (Gefen et al., 2012). However, differences were not evident for the distributions of amyloid plaques, consistent with previous work that suggests cognitive deficits in aging have a stronger relationship with the presence of neurofibrillary tangles than amyloid plaques (Guillozet et al., 2003).

Regarding integrity of deep-brain structures, the hippocampus has been a critical area of focus in the pathology of AD. Early volumetric studies of amnestic AD revealed bilateral reductions in volume of the hippocampus in AD, with atrophy evident to a lesser extent in individuals with aMCI (Shi et al., 2009). Studies reveal a slight trend towards greater volume loss in left hemisphere relative to right hemisphere, though longitudinal studies show this relationship disappears as the disease progresses (Barnes et al., 2005). In a recent study of the hippocampus in non-semantic PPA, Christensen et al. (2015) observed patterns of inward deformation and volume reduction in the hippocampus for the patient group, though the pattern was asymmetrical with the left hemisphere demonstrating more pronounced changes. Interestingly these patterns related to memory performance even in the absence of memory impairments. Overall, deep-brain nuclei are impacted by the presence of AD pathology and may also contribute to the clinical presentation of the disease.

Thalamic Integrity and AD

As previously mentioned, much of the literature on neuroanatomical change in AD has focused primarily on atrophy of medial temporal regions, such as the hippocampus and entorhinal cortex, given their hypothesized role in the formation and maintenance of memory function; research on changes in subcortical regions are relatively fewer by comparison. One critical deep-brain structure that is densely interconnected with the cortex is the thalamus, which functions as a major relay and integration component for the brain. As a major connecting hub for most neural networks, the thalamus is often considered central to the integration of information necessary for sensorimotor and cognitive functions before communicating to the cerebral cortex (Halassa & Sherman, 2019).

Studies have demonstrated the presence of neurofibrillary tangles and beta amyloid plaques in the thalamus early in the AD process (de Jong et al., 2008). Several studies have demonstrated vulnerability of the thalamus to the pathological processes of AD (de Jong et al., 2008; Cherubini et al., 2010; Teipel et al., 2007; Karas et al., 2003). Specifically, reductions in thalamic volume are commonly observed in the context of AD, and found to relate to impaired global cognition, suggesting that the thalamus may play a role in the clinical presentation of these individuals (Ferrarini et al., 2008; de Jong et al., 2008). Other studies reveal bilateral thalamic volume reductions in both aMCI and AD patients relative to controls, but no difference between the patient groups (Pedro et al., 2012). One study comparing those with aMCI that both did and did not convert to AD found that atrophy was evident in the left thalamus for both converters and non-converters (Chetelat et al., 2005). Overall, it appears gross measurements of thalamic volume are able to capture some aspects of pathology in neurodegenerative conditions regardless of severity of impairments.

Studies of brain morphology using shape analysis are increasingly being utilized as sensitive measures for characterizing structural changes relative to traditional volumetric analyses as these techniques allow for the identification of small and subtle changes along a high-dimensional surface (Hahn et al., 2016). One study utilizing surface-based measurements of thalamic integrity observed bilateral inward shape deformation patterns in regions of the anterodorsal nucleus, pulvinar, and intralaminar nucleus in amnestic AD (Zarei et al., 2009). In addition, the left thalamus was observed to have atrophy at the anterior and posterior ends, as well as in ventral aspects, while the right thalamus demonstrated atrophy anterior regions in both the ventral and dorsal aspects (Zarei et al., 2009). A recent study investigating thalamic integrity

in aphasic AD demonstrated significant inward deformation in bilateral ventral and dorsal regions and outward deformation in left medial regions (Paxton, 2019).

Thalamus and Naming

The role of the thalamus in language functioning has been debated for decades (Crosson, 1985). Evidence for the neural basis of these language processes is evident through lesion studies, examination of activation patterns during language tasks, and investigations into structural changes that relate to impaired language functioning. Some of the earliest evidence for a link between language and thalamic integrity comes from studies of thalamic aphasia as a result of vascular lesions to the thalamus. However, the exact nature of language deficits and the course of the impairments is variable across early studies (Crosson, 1985). Nonetheless, language impairments resulting from thalamic stroke provide valuable insights into the function of the thalamus. Kuljic-Obradovic (2003) examined the clinical presentation of individuals with aphasia due to thalamic stroke relative to stroke in other subcortical areas to determine whether localization of the subcortical lesion affected the nature of language deficits. The study found that individuals with thalamic stroke presented with the most severe naming deficits and frequent verbal paraphasias, but with preserved fluency, sentence length and grammar, and repetition. Furthermore, specific thalamic nuclei have been found to relate to various aphasic symptoms, including the left anterior thalamus (Fritsch et al., 2020), and the pulvinar due to its temporo-parietal projections (Wahl et al., 2008). Previous work from our group demonstrated that abnormalities in thalamic shape of the anterior and pulvinar nuclei strongly related to impaired naming performance in individuals with aphasic AD relative to any other language deficit (Paxton, 2019). In particular, left anterior and left pulvinar nuclei were most notable in this relationship with naming performance.

The incidence of aphasia due to thalamic lesions is mixed, with numbers ranging from 15% (Mori et al., 1995) to 51% (Osawa & Maeshima, 2016) to 87.5% (Karussis et al., 2000). It is possible that these discrepancies are due to several differences in methodological approach, including characteristics of the lesion, type of image analysis, and/or type of language deficits. Specifically, one study found that 72.2% of individuals with lesions isolated to the left thalamus exhibited aphasic symptoms characterized by naming problems, with only 1 of 2 individuals exhibiting naming problems due to right hemisphere thalamic lesions (De Witte et al., 2011). Furthermore, the role of the thalamus in various language tasks has been supported by several functional activation studies. Of the studies examining activation patterns during naming tasks in healthy individuals, it was observed that the left thalamus was predominantly involved (Garn et al., 2009). A review by Llano (2013) revealed 5 examples of studies that measured thalamic activation with object naming tasks. Results provide overwhelming support for left greater than right involvement of the thalamus in various naming tasks including silent and overt naming.

In sum, it is well established that aphasia syndromes are a possible consequence of thalamic lesions, though not guaranteed. What is relatively unknown are the specific mechanisms involved in which clinical presentation is expressed when thalamic damage occurs, and if language difficulties are a core or uncommon feature.

Thalamus and Memory

The thalamus has also been extensively explored for its role in memory, particularly in the context of various dementia syndromes. Two thalamic areas that have historically been proposed to be involved in memory impairment include the mediodorsal and anterior nuclei. The mediodorsal nucleus is implicated due to its connections with the perirhinal cortex (Danet et al., 2015), and the anterior nucleus is for its role in Papez circuit and connections with the

hippocampus (Danet et al., 2015). Studies of thalamic lesions indicate that damage to the mammillothalamic tract (MTT) results in an amnestic syndrome, whereas damage to other thalamic regions, including anterior nuclei, mediodorsal, and intralaminar regions, may contribute to memory deficits in various ways (van der Werf et al., 2003). Consistent with this finding, it was determined that combined lesions to the MTT and internal medullary lamina produces an amnestic syndrome by disrupting connections between the medial temporal lobe and the thalamus (Carlesimo et al., 2011; Aggleton & Brown, 1999). With regard to the neuroanatomy of these circuits, the MTT runs adjacent to the medial thalamus, making it difficult to isolate from anterior and mediodorsal nuclei in lesion studies. A recent study by Danet et al. (2015) sought to clarify the resulting clinical presentation based on specific nuclei and found that isolated lesions of the mediodorsal nucleus (in the absence of lesions to the anterior nucleus) resulted in impaired recall. Furthermore, of those individuals with additional damage to the MTT, memory impairment was more severe. In contrast, other studies found that lesions to the mediodorsal nucleus alone did not produce deficits in recognition or recall (van der Werf et al., 2003). Thus, it remains unclear whether specific nuclei account for memory deficits or whether damage to fibers connecting the thalamus and the medial temporal lobe explain the presentation of amnestic syndromes in some individuals.

In the context of neurodegenerative disease, one study observed volumetric differences (atrophy) in the left thalamus related to delayed verbal memory performance in individuals with aMCI and AD, whereas volume changes in the right thalamus were related to global cognitive functioning (Pedro et al., 2012). The involvement of language in the performance of memory increases the difficulty of establishing brain-behavior relationships with these cognitive processes, thus left thalamic findings in these studies may be a product of one or combination of

both functions. Based on these findings, it is likely that although damage to the thalamus results in amnestic and aphasic syndromes, there may be a different pattern of atrophy associated with either syndrome.

Thalamocortical Networks

To better understand the cognitive impairment that results from thalamic lesions, several theories have been proposed that implicate the primary cortical language areas. One explanation is based on the idea of diaschisis, which involves the depression of network activity downstream from a known lesion (Karussis et al., 2000). Studies investigating this theory have found limited evidence for decreases in cerebral blood flow and metabolism in damaged areas and ipsilateral and contralateral cortical areas (Karussis et al., 2000; Baron et al., 1992; Perani et al., 1987).

Another theory proposed as an explanation for subcortical aphasia is the disconnection syndrome, which involves the cortical effects of damage to certain thalamic areas that communicate with cortical areas (Geschwind, 1965; Karussis et al., 2000). Thus, when regions of the thalamus (i.e., pulvinar) that communicate to known cortical language areas (i.e., temporo-parietal junction) are lesioned, the network is disconnected, and language deficits are likely to occur. This theory also explains the absence of aphasia in some individuals with thalamic lesions, as the damaged areas of the thalamus are involved in different cognitive loops, leading to other syndromes that involve areas of the cortex that are not implicated in language functioning (Karussis et al., 2000).

The relationship between language deficits and various corticothalamic connections is fairly well established. In a series of studies, thalamic and cortical scalp electroencephalographic (EEG) activity was recorded during a word matching task and found that activation patterns in both regions were related, with specific involvement of dorsomedial nucleus activity preceding

the pulvinar (Kraut et al., 2003; Slotnick et al., 2002). It was suggested that the pulvinar engages after semantic searching and involves the integration of detected features necessary for retrieval of the object's name (Kraut et al., 2003).

Statement of the Problem

AD pathology, defined by intracellular neurofibrillary tangles and extracellular beta-amyloid plaques, can result in distinct clinical phenotypes that are differentiated based on the area of initial cognitive decline. Namely, some individuals with AD pathology present with initial and progressive dissolution of memory functioning – amnestic AD – while others present with initial and progressive dissolution of language functioning – aphasic AD. Despite the presence of similar underlying pathology, the current study will seek to determine whether there are dissociating anatomical features between these clinical phenotypes in order to assist with the identification, diagnosis, and management of these disease variants. The overarching aim of this project is to characterize thalamic integrity in two known AD pathology clinical phenotypes – namely the aphasic and amnestic variants – and relate it to various aspects of their cognitive presentation.

Aim 1: Quantify and compare thalamic volume and shape features in individuals with amnestic AD and aphasic AD against healthy control participants. It is *hypothesized* that individuals with amnestic AD will exhibit a volumetric reduction and pattern of localized volume changes, represented by abnormal shape deformation in mediodorsal and anterior regions relative to individuals with aphasic AD and healthy control participants.

Aim 2: Examine how thalamic atrophy relates to deficits in language and memory performance in aphasic AD and amnestic AD, respectively. It is *hypothesized* that localized volume loss in pulvinar and anterior nuclei will relate to specific deficits on confrontation naming in individuals

with aphasic AD, while localized volume loss of the anterior nucleus will relate to memory performance in amnestic AD.

Methods

The current study utilized archival data from the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at Northwestern University Feinberg School of Medicine.

Participants

Twenty-five patients with aphasic AD were included in this study, each with a root diagnosis of non-semantic PPA subtypes (logopenic: n = 11; agrammatic: n = 11; mixed/other: n = 3) and determined pathology characterized by excessive beta amyloid (Aβ+) burden upon autopsy. The diagnosis of PPA was made by a team consisting of a behavioral neurologist and a neuropsychologist and was based on established diagnostic criteria (Gorno-Tempini et al., 2011) from information obtained during a clinical interview, cognitive testing with the Uniform Data Set of the National Institute on Aging Alzheimer's Disease Centers program, and review of diagnostic tests (MRI and PET scans). The current project excluded the semantic PPA subtype given both the underlying neuropathology and language profile of these individuals differs from the logopenic and agrammatic subtypes (Rohrer et al., 2012). Consistent with previous work (Rogalski et al., 2019; Martersteck et al., 2020) this is a focused study of only non-semantic PPA due to excessive beta amyloid burden ($PPA^{A\beta+}$), also referred to as the aphasic variant of AD. Individuals were included in the study only if they demonstrated underlying AD pathology as measured by PET-amyloid imaging and post-mortem evaluation. Participants were recruited from the Primary Progressive Aphasia Program at Northwestern University Feinberg School of Medicine. Protocol was approved by the Institutional Review Board of Northwestern University

and informed consent was obtained before evaluation. All participants were right-handed and individuals with serious medical conditions were excluded.

Twenty-one patients with a clinical diagnosis of DAT were included in this study with similar gender and education level. The diagnosis of DAT (amnestic AD) was made based on established diagnostic criteria (McKhann et al., 2011) using information obtained during a clinical interview, cognitive testing, and review of diagnostic tests (PET scan). Participants were recruited at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease and was approved by the Institutional Review Board of Northwestern University; informed consent was obtained before evaluation. All participants were right-handed and individuals with serious medical conditions were excluded.

Forty-four cognitively healthy control participants (CON) of similar gender and education level participated in the study.

Cognitive Assessment

All individuals with aphasic AD were administered a full language battery. The Western Aphasia Battery (WAB) includes tests of auditory comprehension, confrontation naming, repetition, and spontaneous speech, to assign a global Aphasia Quotient score (Kertesz, 2007). The Northwestern Anagram Test (NAT; http://www.soc.northwestern.edu/NorthwesternAnagramTest/) is utilized as a measure of syntax. This test requires patients to order single words, each printed individually, to create a sentence describing actions in a presented picture. The Peabody Picture Vocabulary Test (PPVT-4) is used to assess single word comprehension (Dunn & Dunn, 2007). This test requires patients to point to one of four images that demonstrate the meaning of a presented auditory word. The Mini-Mental State Exam (MMSE; Folstein et al., 2004) is used to assess global functioning. The

current study utilized confrontation naming performance using the BNT (Kaplan et al., 1983). The BNT requires patients to correctly name presented images with possible scores ranging from 0-60. Reliability estimates for the BNT are approximately r = .91 - .92 and performance is correlated with performance on other reading/language measures (Harry & Crowe, 2014).

Individuals with amnestic AD were administered the Alzheimer's Disease Center's Uniform Data Set (UDS) cognitive battery from the National Institute on Aging (http://www.alz.washington.edu; Weintraub et al., 2009). The UDS includes the Mini-Mental State Examination (MMSE) as a measure of dementia severity (Folstein et al., 2004). Attention tests include digit span forward and backward from Wechsler Memory Scale- Revised (WMS-R; Wechsler, 1987). Tests of processing speed include digit symbol task from Wechsler Adult Intelligence Scale-Revised (WAIS-R; Cummings et al., 1994) and Trail Making Test - Part A (Reitan, 1958). Executive functioning is measured using Trail Making Test – Part B. Language is measured using verbal fluency tasks including animal list generation and vegetable list generation (Morris et al., 1989) and naming tasks including the short 30-item version of Boston Naming Test (BNT; Kaplan et al., 1983). Memory is measured using immediate (LM-I) and delayed (LM-D) recall of the Logical Memory subtest from WMS-R (Story A; Wechsler, 1987). Logical Memory subtest requires patients to immediately repeat two short stories (LM-I) and recall them after a 30-minute delay (LM-D), with possible scores on LM-I ranging from 0-25 and possible scores on LM-D ranging from 0-25. Reliability estimates for the LM-I and LM-D are approximately r = .71 and r = .73, respectively (Theisen et al., 1998).

MR Scanning and Image Processing

All MR scans were acquired using high-resolution 3D T1-weighted MP-RAGE volumes following the ADNI protocol (repetition time, 2300 ms; echo time, 2.86 ms; flip angle, 9°; field

of view, 256 mm) recording 160 slices at a slice thickness of 1.0 mm using a 12-channel birdcage head coil (Jack et al., 2008). Imaging was performed at the Northwestern University Department of Radiology Center for Advanced MRI.

Thalamic Morphology

Consistent with our previous study (Paxton, 2019), image processing of thalamic shape features involved utilization of the FreeSurfer-Initiated Large Deformation Diffeomorphic Metric Mapping pipeline (FS+LDDMM; Khan et al., 2008). This automated mapping procedure provides accurate subcortical segmentation and surface maps of deep brain structures, including the thalamus, across both healthy and disease states (Khan et al., 2008). It accomplishes this by warping target regions for each subject into a template space using diffeomorphic transformations that allow independent matching of surface points to preserve unique surface features. Finally, tessellated graphs were superimposed over each subject image to generate final surfaces (Khan et al., 2008). Localized shape differences were characterized using principal components analysis (PCA) to reduce the high dimensionality of the data, resulting in the generation of an orthogonal set of eigenvectors (e.g., principal components) that represent shape variation in both thalamic hemispheres (Beg et al., 2005). The majority of variation in these surfaces (89%) was defined by the first 10 eigenvectors per hemisphere.

Thalamic nuclei of interest include pulvinar, mediodorsal, and anterior regions and were delineated in MR space using previously published landmarking procedures (Cobia et al., 2017). The amount of surface displacement (in mm) from a common template was used as a representation of localized volume loss (inward deformation) or volume exaggeration (outward deformation) and this displacement was averaged across all vertices within each region.

Biomarker Status

Biomarker status was used in the current study to identify patients in aphasic AD and amnestic AD groups according to presence of AD pathology. PET imaging was performed on a Siemens Biograph 40 TruePoint/TrueV PET-CT system. A computed tomography scan was acquired for attenuation correction followed by a 20-min dynamic PET acquisition 50 minutes after administration of 370 MBq F-florbetapir. Visual interpretation of each florbetapir PET scan was used to determine if each scan was elevated (Aβ+) or not elevated (Aβ-; Rogalski et al., 2019). Individuals were considered Aβ+ if there was increased retention of the tracer in the cortical gray matter.

Statistical Analyses

Thalamic Volume Comparison

A repeated measure two-way analysis of covariance (RM-ANCOVA) was conducted to compare thalamic volume, with group status (amnestic AD vs. aphasic AD vs. CON) as the fixed effect, hemisphere (LH vs. RH) as the repeated measure, and age and STV as covariates.

Thalamic Shape Comparison

To investigate shape differences across groups, a repeated measure multivariate analysis of covariance (MANCOVA) model including the 10 averaged eigenvectors, with thalamic hemisphere as the repeated measure and age and STV as covariates, was conducted. If a main effect for group was significant, follow-up univariate ANCOVAs were then conducted to identify significant differences between each group (amnestic AD vs aphasic AD, amnestic AD vs CON, aphasic AD vs CON). A RM-ANCOVA was conducted to compare thalamic morphology for each thalamic nuclei of interest, namely pulvinar, mediodorsal, and anterior, with age and STV as covariates.

Visualization of shape deformation patterns was accomplished by constructing maps of the composite surface of the thalamus at every graphical vertex. Shape displacements were estimated at each surface point as the difference between the means, as measured by individual t-tests at each vertex, of the group vectors in magnitude. Inward and outward displacements, or deformations, are estimated as representations of localized volume loss or exaggeration at the neurobiological level (Hanko et al., 2019). Random Field Theory (RFT) was applied to control for multiple comparisons at a cluster-forming threshold of 0.01 (Flandin & Friston, 2015).

As noted below, age differed significantly between groups and accounting for these differences in subsequent statistical models is an important consideration. Consistent relationships between age and neuroanatomical volumes for total brain and individual structures (except the brainstem and 4th ventricle) have been established, accounting for between 34% and 71% of the variance in cerebral volume in aging (Walhovd et al., 2011). The current study demonstrated a correlation of r = -.30 between STV and age. Both age and STV were included as covariates in ANOVA models to account for the effects of aging. For surface shape maps utilizing t-tests the cubic root of STV was applied to each vertex (given the 3-dimensional nature of the data) to account for the effects of brain age.

Relationships with Neuropsychological Measures

A region of interest (ROI)-based approach was used to investigate relationships between thalamic nuclei and language performance. Thalamic ROIs (anterior and pulvinar) were chosen based on our previous study that demonstrated patterns of inward deformation in aphasic AD that related to confrontation naming performance (Paxton, 2019), as well as known involvement of the anterior nucleus in Papez circuit that is hypothesized to subserve memory performance (Danet et al., 2015). The ROIs included all relevant vertices in these nuclei according to

identified landmarks. Surface displacement was calculated as the difference between the mean surface value (calculated as the average of deformation values for all subjects in the study) and each individual subject's surface at each vertex. These values were then averaged into a mean subcortical shape displacement for each nucleus. Pearson bivariate correlation coefficients were calculated to evaluate relationships between mean shape displacement of thalamic nuclei and memory (as measured by raw LM-D and LM-I scores) in amnestic AD, and with confrontation naming (as measured by raw BNT scores) in aphasic AD (Paxton, 2019). A false discovery rate (FDR) correction was applied at $q = 0.05$ to control for multiple comparisons (Benjamini & Hochberg, 1995).

Post-hoc sensitivity analysis indicates that, given the proposed models and number of participants (amnestic AD n = 21, aphasic AD n = 25, control n = 44), with set levels of $\alpha = 0.05$, power = 0.80, and an observed correlation between repeated measures of .50, RM-ANCOVAs for volumetric comparisons were powered to detect at minimum a critical of F = 3.10. The MANCOVAs for shape comparisons were powered to detect at minimum a critical of F = 3.10. For correlations between neuropsychological performance and thalamic deformation, the amnestic AD (n=20) group was powered to detect at minimum *r* values of (-).44 and the aphasic AD (n = 25) to detect at minimum *r* values of (-).39.

Results

Participants

Table 1 shows demographic data for aphasic AD, amnestic AD, and healthy control groups. There was a significant main effect for group in age [$F(2,87) = 27.50$, $p < .0001$], with follow-up t-tests revealing significant differences between amnestic AD and aphasic AD [$t(45) = 5.26$, $p < .0001$], amnestic AD and healthy control participants [$t(65) = 7.35$, $p < .0001$].

There was no significant age difference between aphasic AD and control participants [$t(69) = 1.57$, $p = .27$]. There were no significant differences between groups for gender [χ^2 (2, N = 90) = 1.25, $p = .54$] and education [F(2,87) = 0.56, $p = .57$].

Table 1. Subject Characteristics by Group

		Aphasic AD, n = 25	Amnestic AD, n = 21	Control, n = 44	P values
Female/Male	(% female)	9/16 (36.0)	11/10 (52.4)	19/25 (43.2)	.54
Age (years)	Mean (SD)	66.7 (6.3)	78.4 (9.6)	64.2 (6.4)	<.0001†
Education (years)	Mean (SD)	16.8 (2.3)	16.0 (4.4)	15.9 (2.3)	.57
BNT (raw)	Mean (SD)	40.8 (13.5)	23.24 (7.28)	58.56 (1.34)	<.001β
	Range	13-59	4-30	55-60	
LM-I (raw)	Mean (SD)		4.9 (3.7)		
	Range		0-13		
LM-D (raw)	Mean (SD)		2.0 (3.0)		
	Range		0-9		

*Note: Only available neuropsychological data is reported. A 30-item version of BNT was utilized for amnestic AD and a 60-item version for aphasic AD and control participants. Thus, direct BNT comparisons for amnestic AD are not included. Abbreviations: BNT: Boston Naming Test, LM-I: Logical Memory Immediate Recall, LM-D: Logical Memory Delayed Recall
† amnestic AD > aphasic AD ($p < .0001$); amnestic AD > CON ($p < .0001$)
β CON > aphasic AD ($p < .0001$)

Thalamic Volume Comparison

Results from the RM-ANCOVA model with age and STV as covariates revealed no significant main effect for group [F(2,85) = 0.66, $p = .52$] or hemisphere [F(1,85) = 0.13, $p = .72$] in thalamic volume. Furthermore, there was no hemisphere-by-group interaction effect [F(2,85) = 2.55, $p = .08$] (see Table 2).

Table 2. Thalamic Volumes (mm^3)

	Aphasic AD, n = 25	Amnestic AD, n = 21	Control, n = 44	P values
R Thalamic Volume: Mean (SD)	6562.5 (94.2)	6451.0 (124.7)	6714.6 (76.3)	.20
L Thalamic Volume: Mean (SD)	6322.4 (96.3)	6353.1 (127.6)	6384.3 (78.0)	.88
STV: Mean (SD)	953291.2 (86834.1)	895245.5 (86506.0)	961396.8 (87598.6)	.02†

Abbreviations: STV: Supratentorial Volume
† CON > amnestic AD ($p = .01$)

Thalamic Shape Comparison

Separate MANCOVA models, with age and STV as covariates, were conducted for thalamic shape comparisons using the first 10 eigenvectors (i.e., principal components) in each hemisphere. Significant main effects for group in both the left [$F(20, 154) = 2.61$, $p < .001$] and right [$F(20,154)= 2.26$, $p < .01$] hemispheres were observed. Follow-up ANCOVAs, with age and STV as covariates, revealed a significant difference between CON and aphasic AD in left [$F(10,56) = 2.16$, $p = .03$] and right [$F(10,56) = 3.99$, $p < .001$] hemispheres and a significant difference between CON and amnestic AD in the left [$F(10,52) = 5.99$, $p < .001$] hemisphere. No significant differences were found between aphasic AD and amnestic AD, or between CON and amnestic AD in right hemisphere.

Separate RM-ANCOVAs, with age and STV as covariates, were also conducted on average shape deformation of the specific thalamic ROI-based nuclei. There were no significant main effects for hemisphere [anterior: $F(1,85) = 0.84$, $p = .36$; mediodorsal: $F(1,85) = 0.22$, $p = .64$; pulvinar: $F(1,85) = 0.71$, $p = .40$] or group for all nuclei [anterior: $F(2,85) = 3.01$, $p = .06$; mediodorsal: $F(2,85) = 0.93$, $p = .40$; pulvinar $F(2,85) = 1.44$, $p = .24$]. There were no

significant hemisphere-by-group interactions for anterior [$F(2,85) = 0.59$, $p = .55$], mediodorsal [$F(2,85) = 0.09$, $p = .10$], or pulvinar [$F(2, 85) = 0.86$, $p = .43$] nuclei.

Surface displacements of the thalamus were scaled using the cube-root of STV to account for the effect of brain age. The resulting RFT-corrected vertex-wise surface shape comparisons revealed patterns of inward deformation on bilateral ventral and dorsal regions for both amnestic AD and aphasic AD groups relative to control participants. Specifically, the aphasic AD group (Figure 1A) exhibited inward deformation across lateral dorsal and lateral posterior nuclei, extending from dorsal aspects of pulvinar to dorsal aspects of the anterior nuclei in left and right hemispheres relative to control participants. A small patch of inward deformation was also evident on the ventral surface of both hemispheres in aphasic AD.

The amnestic AD group (Figure 1B) exhibited more pronounced patterns of deformation relative to control participants. Specifically, inward deformation was evident across the entire ventral and dorsal surface bilaterally, including much of the pulvinar and anterior nuclei. Preserved aspects include patches of medial and lateral aspects of the thalamus, bilaterally.

Finally, comparison of AD phenotypes (Figure 1C) indicates patterns of inward deformation in amnestic AD relative to aphasic AD. Specifically, inward deformation is evident on the poles of bilateral pulvinar nuclei, with right slightly greater than left deformation. Additionally, ventral aspects of the anterior nuclei, bilaterally, indicate inward deformation in amnestic AD that extends ventro-laterally to the bilateral pulvinar nuclei. No differences were observed between phenotypes across the dorsal surface of bilateral thalami, including the lateral posterior and lateral dorsal nuclei.

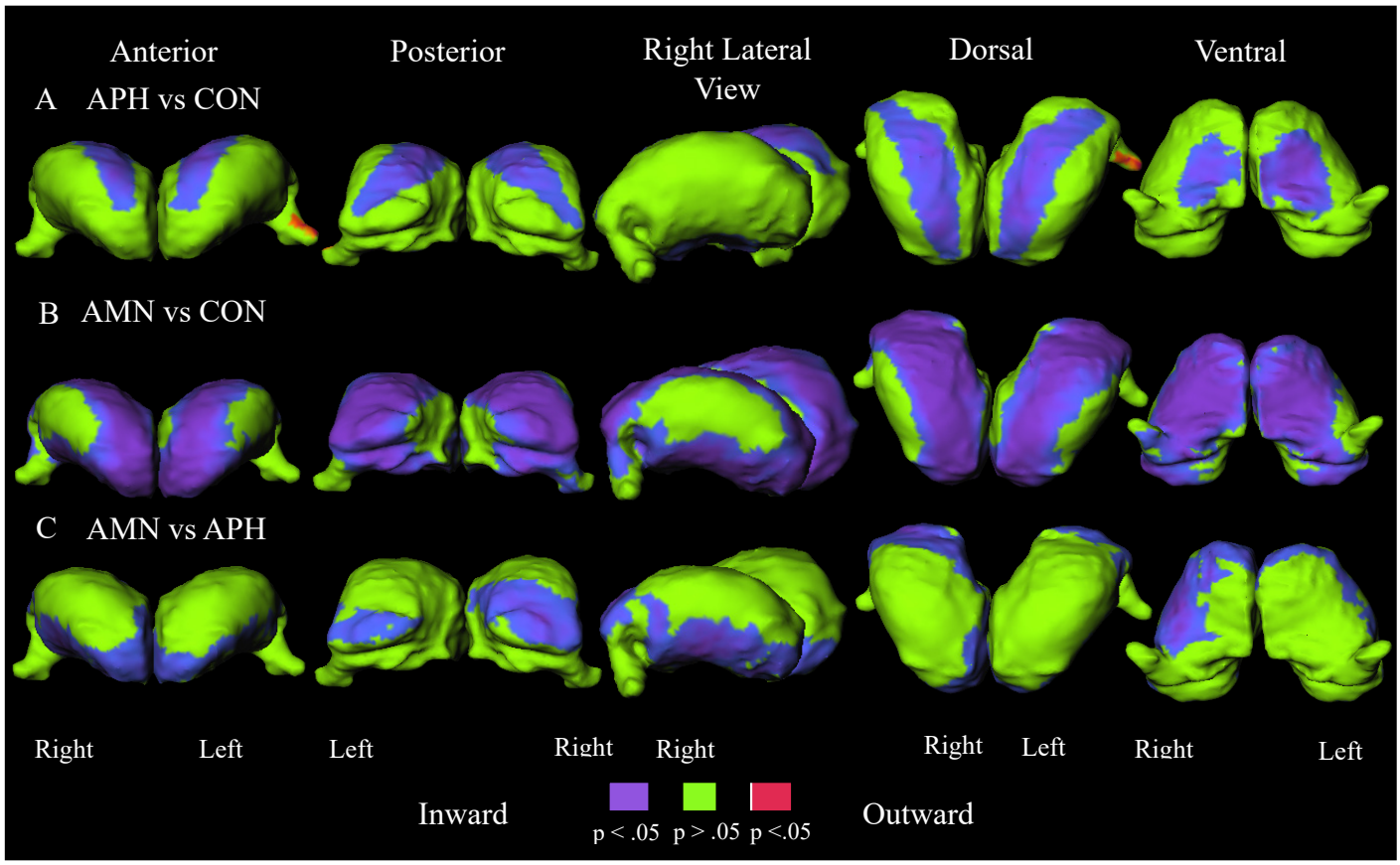

Figure 1. Shape contrast t-maps between groups. Cooler shades (purple) demonstrate greater inward deformation and warmer shades (red) demonstrate greater outward deformation in A) Aphasic AD (APH) subjects relative to control participants (CON), B) Amnestic AD (AMN) subjects relative to control participants, and C) Amnestic AD subjects relative to Aphasic AD subjects. All maps are corrected using RFT to account for multiple comparisons.

Relationships Between Thalamic Shape and Cognition

Data screening revealed one subject in the amnestic AD group with values on memory measures that were considered outside the range of possible scores and were not used for ROI comparisons. Table 1 shows the descriptive data for neuropsychological measures in aphasic AD and amnestic AD groups. A significant difference was observed between aphasic AD and control participants [$t(64) = 8.39$, $p < .0001$]. Of note, aphasic AD group was administered a 30-

item version of BNT. Thus, direct comparisons with this group were not included. Other comparisons were not available due to differences in test administration between groups.

Mean deformation scores in each of the nuclei of interest – pulvinar, mediodorsal, anterior – were correlated against performance on select language measures – confrontation naming – for aphasic AD, and memory measures – LM-I and LM-D – for amnestic AD. Within the aphasic AD group, lower confrontation naming scores were significantly correlated in the positive direction with inward deformation in left pulvinar ($r = .59$, $p < .01$), right pulvinar ($r = .55$, $p < .01$), left anterior ($r = .50$, $p = .01$), and right anterior ($r = .49$, $p = .01$; see Table 3) thalamic nuclei. Within the amnestic AD group, lower LM-D was significantly correlated in the positive direction with inward deformation in left anterior ($r = .46$, $p = .04$; see Table 3) thalamic nuclei. All significant correlations survived the FDR correction for multiple comparisons (see Figures 3 and 4). No significant correlations were found for the mediodorsal nucleus or for LM-I.

Table 3. Correlations (*r*) Between Neuropsychological Measures and Mean Deformation of Thalamic Nuclei by Hemisphere

	Aphasic AD, n = 25	Amnestic AD, n = 20	
	BNT	LM-I	LM-D
L Pulvinar	.59**	.24	.40
L Mediodorsal	.05	.01	.11
L Anterior	.50*	.26	.46*
R Pulvinar	.56**	.18	.30
R Mediodorsal	.12	-.03	-.16
R Anterior	.49*	.10	.44

Abbreviations: BNT: Boston Naming Test, LM-I: Logical Memory Immediate Recall, LM-D: Logical Memory Delayed Recall,
*$p < .05$, **$p < .01$

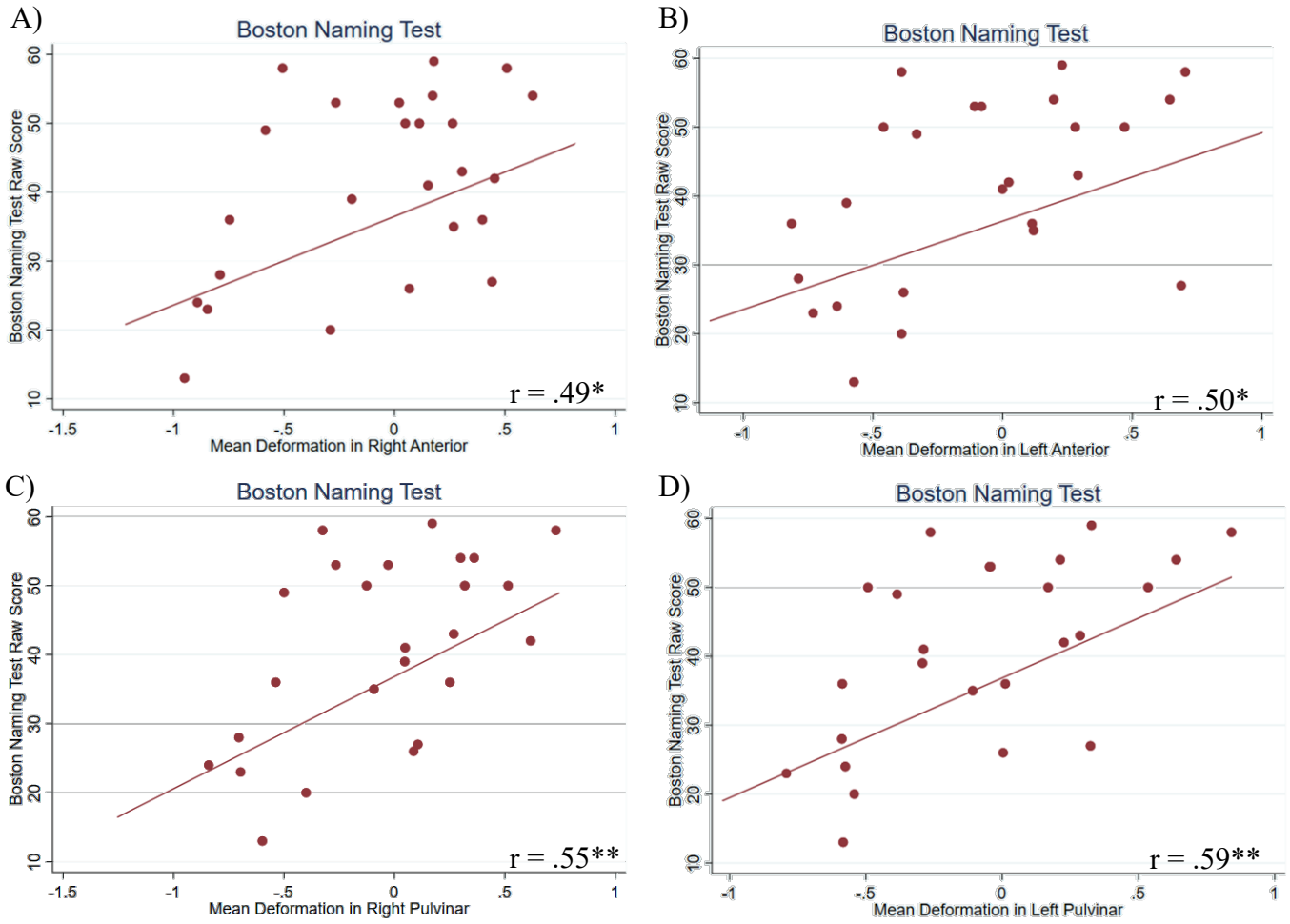

Figure 2. Correlation between thalamic shape scores and language performance within the aphasic AD group that survived FDR correction. Higher BNT scores indicate a greater performance on confrontation naming. Shape scores that are more positive represent outward deformation relative to healthy control participants whereas more negative scores represent inward deformation relative to healthy control participants. A, B) Correlation between thalamic shape scores in the right (A) and left (B) anterior nuclei and BNT raw score. C, D) Correlation between thalamic shape scores in the right (C) and left (D) pulvinar nuclei and BNT raw score. Abbreviations: BNT = Boston Naming Test

*$p < .05$, **$p < .01$

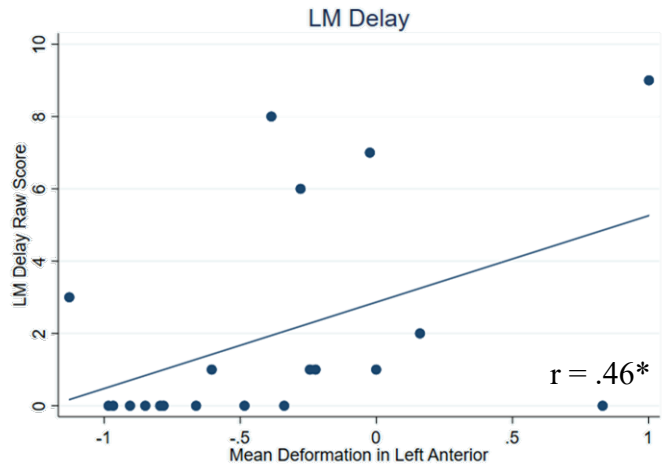

Figure 3. Correlation between thalamic shape scores in the left anterior nuclei and LM-D raw score. This was the only correlation between thalamic shape score and memory performance within the amnestic AD group that survived FDR correction. Higher LM-D scores indicate a greater performance on memory. Shape scores that are more positive represent outward deformation relative to healthy control participants whereas more negative scores represent inward deformation relative to healthy control participants. Abbreviations: LM-D = Logical Memory Delayed Recall

*$p < .05$

Discussion

Neuroanatomical changes involved in AD pathology have been widely studied, particularly as they relate to cognitive functioning. However, the mere presence of AD pathology does not result in a unitary clinical phenotype across all individuals. Many aspects of the disease and its relationship to atypical behavioral presentations remain understudied (Gefen et al., 2012). Recent focus has been drawn to cortical dissociation of phenotypes, namely aphasic variant of AD and amnestic variant of AD. Specifically, unique areas of cortical atrophy in amnestic AD include bilateral medial temporal regions whereas individuals with aphasic AD demonstrate prominent atrophy of left hemisphere perisylvian areas (Gefen et al., 2012; Rogalski et al.,

2011a, Bakkour et al., 2013); these established cortical atrophy patterns align with areas critical to memory and language performance, respectively. However, adequate delineation of neuroanatomical changes should also consider the complexity of neural networks, including the impact of subcortical structures such as the thalamus. The thalamus is known for its many reciprocal cortical connections as well as its role in memory circuitry and language performance (Crosson, 2013; Carlesimo et al., 2011). The present study sought to characterize thalamic integrity using volumetric and high-dimensional shape analysis procedures in two known AD pathology clinical phenotypes – namely the aphasic and amnestic variants. In the absence of volumetric differences, the current study found patterns of bilateral inward deformation in AD groups relative to healthy control participants, with more pronounced patterns in amnestic AD relative to aphasic AD.

With regard to cognitive functioning, amnestic AD is characterized by gradual onset and initial progressive decline in learning and recall of recently learned information (McKhann et al., 2011). In contrast, aphasic AD is characterized by gradual onset and initial progressive decline in language, specifically with impairments in agrammatism in language production or effortful/halting speech with apraxia of speech (PPA-G subtypes) and/or impaired single word retrieval in spontaneous speech and naming as well as impaired repetition (PPA-L subtypes; Gorno-Tempini et al., 2011). In addition to these areas of subtype-specific language impairment, a shared area of impairment across subtypes in aphasic AD is confrontation naming (Gorno-Tempini et al., 2011; Hurley et al., 2012). To further elucidate the relationship of thalamic pathology and cognitive functioning, relationships were explored between localized atrophy in specific nuclei and performance on tasks of language, as measured by confrontation naming, and memory, as measured by immediate and delayed recall of verbal information. Specific ROIs,

namely pulvinar, anterior, and mediodorsal nuclei, were investigated based on their involvement in known language and memory circuits.

The first aim of the study sought to investigate volumetric and shape differences between AD phenotypes and healthy comparison participants. Results revealed no significant volumetric thalamic differences between groups when accounting for age and STV. This contrasts with findings of bilateral thalamic volume reductions in amnestic AD (Pedro et al., 2012; de Jong et al., 2008; Ferrarini et al., 2008) and aphasic AD (Bocchetta et al., 2018) relative to healthy control participants. Interestingly, bilateral thalamic volume loss was also established in at-risk and pre-symptomatic Alzheimer's Disease relative to healthy controls, suggesting that the thalamus is susceptible to early pathological changes (Ryan et al., 2013). Authors concluded that the thalamus is particularly vulnerable to the pathological processes of AD as also evidenced by the early presence of neurofibrillary tangles and beta amyloid plaques in the thalamus (de Jong et al., 2008). The aforementioned volumetric analyses used multi-atlas segmentation techniques or semi-automatic algorithms to estimate structural volumes in left and right thalamic hemispheres in their entirety. Although reductions in volume have been observed in disease groups relative to control populations, studies investigating the difference between disease groups may require a more nuanced look into thalamic integrity to draw more specific conclusions. That is, thalamic nuclei are uniquely diverse, with at least seven different nuclei groups of various subnuclei, locations, and functions suggesting that ROI-specific findings are required for sensitive investigations of thalamic integrity in clinical populations, particularly as they relate to the exact nature of cognitive change (Keun et al., 2021). For example, previous studies suggest that the bilateral reductions in thalamic volume are meaningful as they relate to global mental status (de Jong et al., 2008). This finding demonstrates that thalamic integrity is broadly impacted in the

Alzheimer's disease process and may relate to cognition broadly. However, the exact impact of degeneration on cognition is not explained by this finding. Additionally, the mere absence of volumetric differences between groups does not preclude the impact of degeneration on cognition.

A recent study by McKenna et al. (2022) supports our methodological focus on morphological features to capture distinct aspects of pathological change as opposed to global measures of thalamic atrophy that are likely to overlook localized volume changes. Similar to the current study, McKenna et al. (2022) sought to dissociate clinical phenotypes of frontotemporal dementia in the thalamus in the context of well-established cortical patterns. Volumetric analyses demonstrated widespread atrophy in all phenotype groups across all thalamic nuclei bilaterally, adding little information about the selective involvement of thalamic nuclei whereas morphometric analyses revealed specific patterns of atrophy in particular regions. For example, PPA-G group demonstrated left-lateralized ventrolateral nuclei atrophy compared to left-lateralized pulvinar atrophy in PPA-S, a pattern that helps to distinguish the language patterns that differentiate these variants of PPA. Namely, authors concluded that ventrolateral nuclei are associated with perseverative, fluency, and articulation errors whereas pulvinar nuclei are associated with naming errors, consistent with other studies.

Similarly, studies investigating other disease groups further support our methodological focus on morphometric analyses. For example, an investigation into the dissociation of schizophrenia and schizoaffective disorder, two disorders of the schizophrenia spectrum, demonstrated thalamic volume reductions in both groups relative to healthy control participants but no difference between disease groups (Smith et al., 2011). Morphometric analyses demonstrated patterns of atrophy in anterior and posterior thalamic nuclei in schizophrenia and

medial and lateral thalamic nuclei in schizoaffective disorder, with overlapping atrophy in mediodorsal and ventrolateral regions of the thalamus (Smith et al., 2011). As previously mentioned, this methodological approach allowed authors to draw associations with cortical regions through known thalamo-cortical networks and provide conclusions regarding its implication for cognitive functioning.

Consistent with these findings, the current study demonstrated prominent morphologic abnormalities of the thalamus that were observed in both phenotype groups relative to healthy control participants and that were present in the absence of volumetric differences. Contrast maps controlling for STV showed a specific pattern of bilateral inward deformation in both AD groups relative to control participants along the dorsal and ventral aspects of the thalamus that extended in an anterior to posterior fashion, with more pronounced changes observed in amnestic AD relative to aphasic AD. More specifically, relative to healthy controls, aphasic AD individuals demonstrated inward deformation in ventral nuclei, internal medullary lamina, as well as small patches of pulvinar and anterodorsal nuclei and dorsal aspects of mediodorsal nuclei bilaterally.

Ventral nuclei consist of the ventral posterior nucleus, critical for relay of sensory information from the body to somatosensory association cortices, and the ventral anterior and ventral lateral nuclei, which are critical for relay of motor information. The pattern of deformation in ventral thalamus was also found in amnestic AD relative to healthy controls, which demonstrated relationships with verbal fluency performance (Low et al., 2019); additionally, ventrolateral atrophy was observed in PPA-G relative to PPA-S (McKenna et al., 2022). Although the ventral nuclear group is considered critical for computational aspects of sensory/motor information, it has also been implicated in more complex cognitive functions. As

mentioned previously, ventrolateral nuclei have been associated with language impairments including perseverations, fluency errors, articulation errors, reduced verbal output, as well as confrontation naming (Ojemann & Ward, 1971; Johnson & Ojemann, 2000; Vilkki & Laitinen, 1974; McKenna et al., 2022). Taken together, these findings are consistent with those of the current study, suggesting that observed language deficits in aphasic AD and amnestic AD may also be explained by changes to the integrity of ventrolateral nuclei.

Relative to healthy controls, amnestic AD individuals exhibited inward deformation in ventral nuclei, dorsal aspects of mediodorsal nuclei, anterior nuclei, internal medullary lamina, and pulvinar, bilaterally. This pronounced pattern of deformation that incorporates several thalamic regions makes nuclei-specific predictions more diffuse; however, of the areas evidencing profound inward deformation patterns, anterior nuclei and medial dorsal nuclei stand out as key components of the limbic thalamus and Papez circuit. This circuit involves communication of the hippocampus with the mammillary bodies, followed by anterior thalamus, the cingulate cortex, parahippocampal gyrus, and finally the hippocampus (Jankowski et al., 2013). The importance of the anterior nucleus has since been well documented for its role in memory performance. Interestingly, volume loss in anterior thalamic nuclei was found to dissociate Korsakoff's, an amnestic syndrome associated with alcohol use from other alcohol-related conditions that do not present with amnesia (Harding et al., 2000). Additionally, an estimated 12% of thalamic infarcts involve anterior thalamic nuclei regions, with many individuals exhibiting profound memory impairments (Carrera & Bogousslavsky, 2006). Although much attention has been devoted to hippocampal involvement in amnestic AD, the hippocampus has dense connections to the anterior thalamic nuclei and researchers are only

recently turning their attention to the thalamus as a possible primary site of neurodegeneration (Aggleton et al., 2016) – the current study supports this shift in attention.

Specifically, the pattern of amnestic AD deformation we observed is consistent with previous studies. For example, Zarei et al. (2010) noted inward deformation in the bilateral internal medullary lamina, mediodorsal, ventral, and anterior nuclei and left pulvinar nuclei in a sample of amnestic AD participants. The authors expanded upon this finding by using tractography to draw two main conclusions – first, they demonstrated connectivity of mediodorsal nuclei with anterior temporal cortex and posterior hippocampus and concluded that this circuitry was a critical component of neurodegeneration in amnestic AD. This is consistent with neuroanatomical connections of the hippocampus with the anterior thalamus as mentioned previously. Second, they found that the thalamic area demonstrating the largest reductions in connectivity was the anterodorsal nucleus. This reduced connectivity corresponded with atrophy of the internal medullary lamina. The authors concluded that reductions of connectivity in the anterodorsal region may be associated with atrophy of the internal medullary lamina, both patterns of which were evidenced in the current study. Insights from stroke case studies also support this finding, with bilateral atrophy in internal medullary lamina and mediodorsal nuclei resulting in severe memory impairment, even in the absence of damage to other aspects of Papez circuit, including mammillary nuclei, mammillothalamic tracts, and medial temporal lobes (Gold & Squire, 2006).

Interestingly, this pattern is also consistent with patterns of left mediodorsal and anteromedial thalamic nuclei of amnestic Mild Cognitive Impairment (aMCI) relative to healthy control participants (Hahn et al., 2016). This study of aMCI is critical in understanding AD, as the rate of conversion from aMCI to amnestic AD is estimated to range from 20% (Lehrner et al.,

2005) to 48.7% (Fischer et al., 2007). The mediodorsal nucleus is characterized as a relay nucleus for association areas in the frontal lobe, with outputs to the prefrontal cortex and cingulate gyrus and involvement in memory functioning. Insights from stroke literature suggest that unilateral mediodorsal atrophy relates to specific patterns of memory impairment, with left-lateralized pattern relating to verbal memory deficits and right lateralized patterns relating to visual memory deficits (Edelstyn et al., 2012). The findings of deformation in aMCI suggest that the changes to the integrity of these nuclei demonstrated in the current study may occur in early stages of neurocognitive disorders, particularly those that may represent even prodromal amnestic AD.

While previous studies (Hahn et al., 2016) demonstrated left lateralized thalamic atrophy patterns, the current study found bilateral changes across pathology groups relative to healthy controls. However, the current study also demonstrated slightly greater right deformation patterns in amnestic AD relative to aphasic AD. Investigations into the symmetry of AD pathology suggest that aphasic AD presents with more neurofibrillary tangles in the left hemisphere compared to symmetric presence of tangles in amnestic AD (Gefen et al., 2012). As mentioned across many studies, neuropsychological investigations demonstrate language impairments and verbal memory deficits predominantly explained by left hemisphere pathology and visual memory deficits predominantly explained by right hemisphere pathology (Edelstyn et al., 2012; Rogalski et al., 2011a). The more symmetric nature of amnestic AD was consistent with direct AD group comparisons in the current study. This finding emphasizes the left-lateralizing nature of aphasic AD when directly compared to amnestic AD and suggests that symmetry may be used as a dissociating feature of AD phenotypes.

Finally, vertex-wise surface maps revealed inward deformation in right ventrolateral regions in the amnestic AD relative to aphasic AD groups, with no other differences observed. As discussed previously, ventrolateral deformation is related to impairments in language functioning and studies of verbal functioning after unilateral ventrolateral thalamotomy indicate that verbal impairments were evident only following left thalamotomy, whereas right ventrolateral thalamotomy produced inattention to cues in the rapid perception of faces on a visual face-matching task, although this performance improved 6-18 months post-operation (Vilkki & Laitinen, 1973). Authors concluded that left ventrolateral thalamus is important in verbal information and the selection of relevant verbal responses whereas the right ventrolateral thalamus is important in visual perception of faces and more complex visual perception processing. Given the language-focused impairments in aphasic AD, preservation of right ventrolateral areas in aphasic AD relative to amnestic AD is supported. The visual processing aspect of the ventrolateral thalamus may be more critical in amnestic AD as it relates to visual learning and memory.

Our second aim examined the influence of thalamic integrity in relevant thalamic nuclei – namely the anterior, pulvinar, mediodorsal – on language in aphasic AD, as measured by confrontation naming; and memory in amnestic AD, as measured by immediate and delayed verbal recall. Previous work demonstrated a relationship between confrontation naming performance and inward deformation in left pulvinar and left anterior thalamic nuclei in aphasic AD, such that a worse confrontation naming performance related to more inward deformation (Paxton, 2019). The current study expanded upon this finding by revealing that poorer performance on confrontation naming was related to more inward deformation in bilateral pulvinar and anterior nuclei. This finding, which supports the role of the thalamus in

confrontation naming, is consistent with investigations into aphasia syndromes that result from thalamic stroke. Specifically, studies suggest that lesions to pulvinar or anterior nuclei produce naming deficits (Maeshima & Osawa, 2018). Some researchers suggest that the mechanism underlying these language impairments is a failure to activate cortical circuits that support object word retrieval due to thalamic lesions (Llano, 2013). The pulvinar is documented as one of the most widely connected thalamic nuclei, communicating with the prefrontal cortex and superior temporal gyrus (Barron et al., 2015). Another theory discussed previously is that of the disconnection syndrome, which refers to the disruption of neural networks as a result of damage to specific thalamic regions (Karussis et al., 2000). That is, the variability in behavioral presentation may be due to the disconnection of different neural networks as opposed to isolated areas of atrophy in the thalamus alone.

The current study also revealed a relationship between left anterior thalamic nuclei in amnestic AD and delayed memory performance, such that a poorer performance for memory was related to greater inward deformation. Broadly, investigations into cognitive performance in Alzheimer's disease revealed that the left volumes of the hippocampus, putamen, and thalamus formed the strongest predictors for global cognition, as measured by cognitive screens (de Jong et al., 2008). With respect to memory specifically, insights from stroke literature focusing on anterior thalamic lesions suggest a profound retrieval deficit on memory testing (Ghika-Schmid & Bogousslavsky, 2000). Interestingly, this pattern is also consistent with aMCI, with verbal learning and memory impairments at this early stage of presumed AD correlating with atrophy in left dorsomedial and left anteromedial thalamic nuclei (Hahn et al., 2016). Additionally, as summarized previously, anterior thalamic nuclei are involved in Papez circuit, with inputs from

mammillary bodies via mammillothalamic tract and outputs to the cingulate gyrus, a circuitry that is critical to memory performance (Hahn et al., 2016).

Although thalamic changes have been established in the conversion from MCI to DAT, recent investigations suggest that there are no clear thalamic volume differences between later MCI stages and DAT, suggesting that conversion to DAT and specific behavioral presentations are due to the atrophy of cortical areas, including the hippocampus in amnestic AD (van de Mortel et al., 2021). Similarly, given the early atrophy identified in anteromedial regions of the thalamus and its connections to the hippocampus, rates of atrophy in these areas may indicate sites of primary and secondary degeneration. That is, it is theorized that neurodegeneration of one structure could initiate the neurodegeneration of a second, connected structure (Stepan-Buksakowska et al., 2014). For example, Liu et al (2019) investigated longitudinal patterns of deformation following subcortical MCA infarction as they relate to verbal memory performance. They found that the change rate of atrophy over 12 weeks in the left thalamus was related to immediate recall. More specifically, morphological analysis revealed inward deformation in ipsilesional (left) anteromedial and patches of lateral dorsal thalamic nuclei regions with known connections to prefrontal, temporal, and premotor cortices. The rate of this atrophy over 12 weeks was correlated with the change in verbal memory recall over that time, such that more inward deformation related to a worse performance on immediate verbal recall. Given that the thalamus is not directly supplied by the MCA, findings further support that thalamic changes reflect secondary degeneration of thalamo-cortical pathways and that these changes in turn relate to declines in verbal memory.

Limitations for the current study relate to methodology. First, inherent with morphology research, inward/outward deformation does not necessarily indicate loss/gain of function, thus

causal claims cannot be made. Second, there is always some inherent error using automated imaging systems and although our approach demonstrates high reliability and accuracy (Khan et al., 2008), there are single image dependencies, indicating some loss of information or resolution from image to image, although this is reduced by image consistency. Third, our pathology groups differed significantly with regard to age, introducing a confound into the analyses. We attempted to address this by including age and STV as covariates in all analyses. However, despite our large sample size for the population of interest and the sensitivity analyses supporting our conclusions, it is possible that findings would be more accurate with a larger sample of age-matched subjects. Finally, effects of the overlap between language and verbal memory cannot be ruled out. Our study would have benefited from the use of visual learning and memory measures to reduce the confound of verbal functioning, particularly in the investigation of amnestic AD.

Our study demonstrated patterns of bilateral inward deformation. However, the mechanism of thalamic involvement and the clarity of its role in distinguishing the phenotypes remains insufficient. In considering the pathological impact of AD on the thalamus, it is critical to understand the cascade of pathological events that result from AD pathology. Braak and Braak AD stages suggested that the thalamus is an early target of AD pathology and likely an antecedent in the process of neurodegeneration throughout the cortex (Xuereb et al., 1991). For example, research reveals that the anterodorsal nucleus is the primary site of degeneration in AD, with up to 80% cell loss in postmortem examinations (Xuereb et al., 1991). Given the early neurodegeneration evidenced in the thalamus, it is possible that investigations into the primary and secondary degeneration processes may help to further clarify pathological impact of AD. Thus, future studies should investigate the functional connections between thalamic nuclei and cortical regions critical in language and memory to further dissociate clinical phenotypes of AD.

Further investigation of the rates of atrophy and connections with cortical regions may help to 1) delineate the potential causal impact of early thalamic degeneration on integrity of cortical areas over time and 2) identify whether thalamic atrophy occurs due to AD pathology irrespective of behavioral presentation, with patterns of cortical atrophy dissociating AD phenotypes more accurately.

Overall, the current study is the first to directly compare thalamic integrity using high-dimensional shape analysis procedures in aphasic and amnestic variants of AD. Its findings reveal significant dorsal, ventral, posterior, and anterior abnormalities of the thalamus in AD phenotypes relative to healthy individuals, with more pronounced changes in amnestic AD relative to aphasic AD, irrespective of age. Furthermore, thalamic integrity related to confrontation naming in aphasic AD and delayed recall in amnestic AD. However, thalamic integrity alone is unable to fully explain the dissociation between aphasic and amnestic phenotypes of AD. Findings contribute to our understanding of the process of AD pathology and provide a direction for future studies that will continue to influence strategies for the identification, diagnosis, management, and treatment of AD phenotypes.

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