2019-06-01

Thalamic Morphology in Non-Semantic Primary Progressive Aphasia

Holly Rochelle Paxton
Brigham Young University

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Holly Rochelle Paxton

A thesis submitted to the faculty of
Brigham Young University
In partial fulfillment of the requirements for the degree of

Master of Science

Derin J. Cobia, Chair
Shawn D. Gale
Michael J. Larson

Department of Psychology

Brigham Young University

ABSTRACT

Thalamic Morphology in Non-Semantic
Primary Progressive Aphasia

Holly Rochelle Paxton
Department of Psychology, BYU
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Background: Primary progressive aphasia (PPA) is a clinical dementia syndrome characterized by impairments in language. The presence of Alzheimer disease (AD) neuropathology has been observed in approximately 40% of PPA cases. Cross-sectional and longitudinal features of cortical atrophy in PPA are emerging but less is known about the integrity of subcortical structures, particularly the thalamus. As a major relay station in the brain, the thalamus is implicated in language functioning given its reciprocal connections with perisylvian regions in the cortex. High-dimensional brain mapping was used to characterize thalamic morphology in individuals with and without non-semantic PPA. Further, shape differences were compared between PPA participants with suspected AD pathology ($PPA^{A\beta+}$) and those without suspected AD pathology ($PPA^{A\beta-}$) as determined by amyloid PET scans. The relationship between shape and specific language deficits were also investigated.

Method: Thalamic integrity was examined in 57 PPA participants relative to cognitively healthy controls (N=44) with similar demographics. 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. Thalamic nuclei of interest included mediodorsal, pulvinar, and anterior regions. General linear models compared differences in thalamic shape between groups. Pearson models characterized relationships between thalamic nuclei and language function.

Results: After controlling for whole brain volume, thalamic volume did not differ between groups [$F(1, 99)=0.80$, $p=0.80$]. However, PPA participants exhibited significant bilateral inward shape deformation in dorsal and ventral regions that extended in an anterior to posterior fashion, and unilateral outward deformation in medial and lateral regions only in the left thalamus relative to controls [$F(9, 91)=5.75$, $p<0.001$, Wilk's $\Lambda=0.64$]. There were no shape differences between $PPA^{A\beta+}$ and $PPA^{A\beta-}$ groups. Pearson models revealed significant correlations between confrontation naming and shape deformation in the left pulvinar ($r=0.59$, $p<0.01$) and left anterior ($r=0.55$, $p<0.01$) thalamic nuclei for the $PPA^{A\beta+}$ group only, such that lower language scores reflected greater localized volume loss.

Conclusions: In the absence of volumetric differences, shape measures were able to capture unique aspects of localized morphologic differences in PPA that corresponded to worse naming performance only in those with suspected AD pathology. Thalamic changes appear to be a contributing and unrecognized component to the presentation and language characterization of PPA.

Keywords: Alzheimer's disease, amyloid-beta, primary progressive aphasia, thalamus

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Dr. Derin Cobia, for the continuous support of my PhD study and research, for his patience, motivation, and immense knowledge. I am grateful that he took a chance on me and provided me the opportunity to be involved in such a great research lab.

My sincere thanks goes to the team at Northwestern University Feinberg School of Medicine, specifically Dr. Emily Rogalski and the Mesulam Center for Cognitive Neurology & Alzheimer's Disease, for allowing me the opportunity to access their immense database and resources. Without their support, encouragement, and insightful comments, this research would not have been possible.

I would like to thank the rest of my thesis committee, Dr. Shawn Gale and Dr. Michael Larson, for their feedback, their endless support, and all their tough questions.

I would like to thank my family - my parents and my fiancé - for supporting me throughout this incredible journey. I am so grateful for their patience, their advice, their unconditional love, their open ears, and their ability to always bring me back from my stress-induced meltdowns. I would not be where I am today without them.

Last but not least, a very special thanks to my brother, Troy Paxton, for always supporting me, believing in me, keeping me humble, and reminding me that it's okay to have a weak moment. He always knew just the kind of support I needed and I can still feel his support in spirit every single day. Thank you for always having my back. I love and miss you so much, broski.

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Thalamic Morphology in Non-Semantic Primary Progressive Aphasia

Introduction

Primary Progressive Aphasia (PPA) is a form of dementia characterized by isolated and progressive dissolution of language functions across various domains. Diagnostic criteria for PPA requires that aphasia is the primary deficit both at onset and during the initial phase of the disease and must be the principal cause of impaired activities of daily living (Gorno-Tempini et al., 2011). PPA is a heterogeneous disorder with individuals experiencing a variety of aphasic symptoms. To capture the heterogeneity of the disorder, three subtypes of PPA have been defined – semantic, nonfluent/agrammatic, logopenic – based on the clinical presentation of language deficits (Mesulam, Grossman, Hillis, Kertesz, & Weintraub, 2003). The current study will focus on the two non-semantic subtypes. Deficits in individuals with non-semantic PPA include, but are not limited to, object naming deficits, comprehension difficulties, agrammatism, impaired repetition of sentences, and semantic paraphasias (Gorno-Tempini et al., 2011). Recent literature has focused on discovering the etiology and describing the underlying neuropathology of this rare neurodegenerative disorder and its subtypes.

With regards to neuroimaging investigations, previous research has identified many cortical abnormalities in PPA. Atrophy of the entire left hemisphere including perisylvian areas of the temporal, frontal, and parietal lobes have been revealed (Rogalski et al., 2011; Gorno-Tempini et al., 2004). Given the isolated language impairments in PPA, research has also been devoted to understanding cortical thinning patterns as they relate to specific language deficits. Frontal atrophy was related to deficits in fluency and grammar, while posterior and temporal atrophy was more related to deficits in sentence structure and object naming (Mesulam et al., 2009). More specifically, a positive correlation was found between semantic processing,

sentence repetition, grammatical processing, and fluency, and left hemisphere areas including temporal pole, superior temporal gyrus, inferior frontal gyrus, and middle frontal gyrus, respectively (Rogalski et al., 2011). Despite our understanding of the cortical features involved in the disorder and its presenting impairments, little research has discovered the role of subcortical structures in the pathophysiology of PPA.

One critical deep-brain structure that is densely interconnected with the cortex and may be related to symptoms of PPA is the thalamus. The thalamus acts as the brain's main sensory relay, coordinating multiple sensorimotor activities and integrating several cognitive functions (Barbas, Garcia-Cabexas, & Zikopoulos, 2013). The role of the thalamus in neurodegenerative disorders has been well established. Individuals diagnosed with Alzheimer's disease (AD) demonstrate a significant reduction in the overall volume of the thalamus that correlates with global cognitive decline, such that the greater reduction in volume, the greater cognitive impairment (de Jong et al., 2008). Localized atrophy of the thalamus has been related to several other disorders of cognitive functions, including schizophrenia, amnestic mild cognitive impairment (aMCI), and AD (Csernansky et al., 2004; Hahn, Lee, Won, Joo, & Lim, 2016; Zarei et al., 2009, respectively). For example, localized volume changes represented by shape deformations in mediodorsal and anteromedial nuclei have been observed in aMCI (Hahn et al., 2016).

With regards to thalamic pathology in neurodegenerative disorders, the presence of AD tangles and plaques has been observed in the thalamus early in the Alzheimer's disease process (de Jong et al., 2008). AD pathology is characterized by intracellular neurofibrillary tangles and extra-cellular beta-amyloid plaques. Although most individuals with PPA show pathology consistent with frontotemporal lobar degeneration (FTLD), including non-Alzheimer tauopathies

and abnormal precipitates of the 43 kD transactive response DNA binding protein TDP-43, about 30-40% of individuals with PPA have suspected AD pathology (Mesulam et al., 2008; Knibb, Zuereb, Patterson, & Hodges, 2005; Rogalski & Mesulam, 2009). Several studies have investigated the incidence of various types of underlying pathology between the subtypes of PPA. However, it is not well understood how the underlying pathology of PPA relates to structural brain changes specifically in the thalamic nuclei.

Investigation of aphasia in stroke patients has provided insight into the role of the thalamus in the performance of various language tasks. Thalamic infarcts are frequently associated with prominent aphasia syndromes including semantic paraphasias, perseverations, and word finding difficulties, despite intact repetition and auditory/verbal comprehension (Crosson, 2013). The role of the thalamus in language has been supported by its extensive cortical communication pathways. Disruptions in language may be due to abnormalities in cortico-thalamic networks (Wahl et al., 2008), suggesting the presence of thalamic abnormalities in PPA reflective of the cortical thinning patterns already found in the trajectory of the disease. Specifically, certain thalamic nuclei - pulvinar, mediodorsal, and anterior - are suggested to be highly involved in language processes due to their dense cortical connections with multimodal association regions (Llano, 2013).

Several lines of functional imaging studies reveal activation in thalamic nuclei during specific language tasks. First, the pulvinar plays a significant role in thalamic aphasias and is extensively connected to language areas of the cortex, including frontal, posterior temporal, and inferior parietal cortices that process syntactic and semantic language (Crosson, 2013; Llano, 2013; Wahl et al., 2008). Furthermore, the pulvinar receives inputs from Broca's area, a structure involved in expressive speech (Crosson, 2013). Activation of the pulvinar is observed during

picture naming tasks and lexical decision tasks while stimulation of the area leads to object naming difficulties (Llano, 2013; Crosson, 2013). Second, the mediodorsal nucleus of the thalamus also receives input from Broca's area and is the relay nucleus for association areas in the frontal lobe (Crosson, 2013; Hahn et al., 2016). Activation of the mediodorsal nuclei has been shown in sentence reading tasks and lexical decision tasks (Mestres-Misse, Camara, Rodriguez-Fornells, Rotte, & Munte, 2008; Ketteler, Kastrau, Vohn, & Huber, 2008). Third, the anterior nucleus is implicated in many circuits and communication networks, including Papez circuit, implicating it in learning and memory (Hahn et al., 2016), a basal ganglia connection loop that activates during word selection (Crosson, 2013), and the pathway from Broca's area to the pulvinar, which first passes through the anterior nucleus (Crosson, 2013). Finally, damage to anterior, pulvinar, and mediodorsal regions result in similar aphasic syndromes (Crosson, 2013).

Given the identified role of the thalamus in language, including its reciprocal connections with language regions in the cortex, it is hypothesized that the thalamus plays a unique role in the pathology of PPA. Due to the heterogeneity of the various subtypes of PPA, the current study will focus on the two non-semantic subtypes that are most similar in presentation – logopenic and nonfluent/agrammatic. Logopenic variant PPA is characterized by deficits in repetition and single-word retrieval in speech and naming, whereas nonfluent/agrammatic variant PPA is characterized by apraxia of speech, and deficits in language production and single word and sentence comprehension (Gorno-Tempini et al., 2011). The overarching aim of the current study is to utilize high-dimensional brain mapping to characterize thalamic shape patterns in non-semantic PPA and relate them to specific language processes that are core features of the presentation of PPA. Given the lack of research on this topic, findings from this study would further our understanding of the role of the thalamus in PPA in general and elucidate the

relationship of specific language deficits to particular thalamic nuclei. In summary, the current study will describe thalamic morphology in non-semantic PPA using MR imaging to determine how thalamic shape features relate to specific language deficits.

Aims and Hypotheses

Aim 1: Quantify thalamic volume and shape features in individuals with non-semantic PPA and compare them against a group of healthy age-matched control subjects. It is hypothesized (H1) that localized volume changes, represented by abnormal shape deformations, will be present in individuals with non-semantic PPA relative to controls.

Aim 2: Compare thalamic volume and shape features between those with and without suspected AD pathology in individuals with non-semantic PPA. It is hypothesized (H2) that individuals with non-semantic PPA and suspected AD pathology ($PPA^{A\beta+}$) will demonstrate greater thalamic deformation relative to those without suspected AD pathology ($PPA^{A\beta-}$).

Aim 3: Determine how atrophy in specific thalamic nuclei, namely pulvinar, mediodorsal, and anterior regions, relates to particular language deficits in individuals with non-semantic PPA. It is hypothesized (H3) that abnormalities in pulvinar, mediodorsal, and anterior nuclei will relate to specific deficits on confrontation naming, syntax, single word comprehension, and repetition.

Method

Participants

Fifty-seven patients with a root diagnosis of PPA and forty-four cognitively healthy controls of similar age, gender, and education level participated in the study. The diagnosis of PPA was made by a team consisting of a behavioral neurologist and a neuropsychologist (M.M and S. W.) and was based on established diagnostic criteria (Gorno-Tempini et al., 2011) from information obtained during clinical interview, cognitive testing with the Uniform Data Set of

the National Institute on Aging Alzheimer Disease Centers program, and review of diagnostic tests (MRI and PET scans). 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. Each participant was administered the Western Aphasia Battery (WAB), including tests of auditory comprehension, confrontation naming, repetition, and spontaneous speech, to assign an Aphasia Quotient score to each individual. Participants with serious medical conditions were excluded.

Neuropsychological Measures

Confrontation naming was assessed using the Boston Naming Test (BNT). This test requires patients to correctly name presented images. Syntax was assessed using the Northwestern Anagram Test (NAT; http://www.soc.northwestern.edu/NorthwesternAnagramTest/), including syntactically simple and complex sentence production. This test requires patients to order single words, each printed individually, to create a sentence describing actions in a presented picture. Single word comprehension was measured using the Peabody Picture Vocabulary Test (PPVT-4). This test requires patients to point to one of four images that demonstrate the meaning of a presented auditory word. Sentence repetition was measured using the repetition subtest of WAB (items 10-15), of which only sentence items were used. All neuropsychological measures were administered by MM and SW.

MR Scanning and ma-FSLDDMM

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.

Image processing of thalamic shape features involved utilization of FreeSurfer-Initiated Large Deformation Diffeomorphic Metric Mapping (FS+LDDMM; Khan, Wang, & Beg, 2008). This automated data analysis procedure was found to improve accuracy of subcortical segmentation, including the thalamus, across several neuropsychiatric diseases (Khan et al., 2008). Localized shape differences were characterized using principal components (PC) analysis to reduce the high dimensionality of the data. This procedure resulted in the generation of an orthogonal set of eigenvectors (i.e., principal components) representative of variation in the shape of the left and right thalamus (Beg, Miller, Trouve, & Younes, 2005). The majority of variation in these surfaces (88.4%) was defined by the first 10 eigenvectors per hemisphere. Thalamic nuclei of interest included mediodorsal, pulvinar, and anterior regions, and were delineated using landmark procedures in MR space (Cobia et al., 2017). The amount of surface displacement (in mm) from a common template was used as a representation of localized volume loss and averaged across all vertices within each zone.

Biomarker Status

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., in press). Individuals were considered Aβ+ if there

was increased retention of the tracer in the cortical gray matter. PET scans revealed Aβ- status when there was preserved gray/white contrast throughout the cortex.

Statistical Analyses

A priori data screening guidelines defined an outlier as any subject with values outside the median plus/minus 2 inner quartile range. Extreme scores for the subjects were recoded to the upper/lower limit of the range. Chi-square and t-tests were used to examine group differences on demographic variables. A repeated measure two-way analysis of variance (ANOVA) was utilized for analysis of thalamic volume, with group status (PPA vs. CON) as the fixed effect and hemisphere (LH and RH) as the repeated measure. To account for whole brain volume, a repeated measures ANOVA was also used with supratentorial volume as a covariate in the model.

To determine whether group comparisons were more appropriate utilizing average shape across hemisphere or conducting on a per hemisphere basis, 10 t-tests were utilized to compare eigenvalues (PC) for each hemisphere. To investigate shape differences across groups, a repeated measure multivariate analysis of variance (MANOVA) model including the 10 averaged eigenvectors, with thalamic hemisphere as the repeated measure. If a main effect for group was significant, follow-up univariate ANOVAs were then conducted to identify significant differences between each group (i.e., $PPA^{A\beta+}$ vs CON, $PPA^{A\beta-}$ vs CON, $PPA^{A\beta+}$ vs $PPA^{A\beta-}$).

Visualization of shape deformation patterns were constructed with 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 of the group vectors in magnitude. Random Field Theory (RFT) was applied to control for multiple comparisons (Flandin & Friston, 2015).

Next, a region of interest (ROI)-based approach was used to investigate relationships between thalamic nuclei and language performance. Thalamic ROIs (i.e., anterior, mediodorsal, pulvinar) included all relevant vertices in specific nuclei according to identified landmarks. Surface displacement was calculated as the difference between the template surface and each individual subject's surface at each vertex; these values were then averaged into a mean subcortical shape displacement for each nuclei. Pearson bivariate correlation models were then used to evaluate relationships between mean shape displacement of thalamic nuclei and each language measure of interest. A false discovery rate (FDR) correction was applied at the level of .05 to control for multiple comparisons.

Results

Participants

Table 1 shows demographic data for PPA and healthy control groups. There were no significant differences in age (t = -1.76, p = 0.08), gender (χ^2 = 0.22, p = 0.64), and education (t = -0.54, p = 0.59) between PPA subjects and controls. Among the PPA group, there were no significant differences in age (t = 0.30, p = 0.77), gender (χ^2 = 0.01, p = 0.99), education (t = -1.67, p = 0.10) and overall WAB Aphasia Quotient (WAB-AQ) scores (t = -0.40, p = 0.69) between $PPA^{A\beta+}$ subjects and $PPA^{A\beta-}$ subjects (see Table 2).

Post-hoc sensitivity analysis indicates that, given the aforementioned analyses and number of participants, with α = .05, power = .80, and a correlation between measures of .50, the present study was powered to detect a critical F of F = 2.70.

Neuropsychological Assessments

MANOVA results revealed a significant difference between PPA and CON subjects on neuropsychological measures, $F(4, 81) = 17.60$, $p < .001$, Wilk's $\Lambda = 0.54$ (see Table 2). PPA subjects performed significantly poorer on every language measure compared to controls.

Within the PPA group, MANOVA models revealed a significant difference between $PPA^{A\beta+}$ and $PPA^{A\beta-}$ subjects on neuropsychological measures, $F(4, 46) = 3.40$, $p = .02$, Wilk's $\Lambda = 0.77$. $PPA^{A\beta+}$ subjects performed significantly worse on confrontation naming (BNT) relative to $PPA^{A\beta-}$ subjects ($p = .04$). There were no other significant group differences on neuropsychological measures between $PPA^{A\beta+}$ and $PPA^{A\beta-}$ subjects.

Thalamic Volume Comparison

Data screening revealed one subject with values that were considered outliers based on previously defined criteria.

Results from the repeated measures ANOVA revealed no main effect of group on whole thalamic volume [mean (SD) = PPA: left = 6346.0 (741.4) mm^3, right = 6619.0 (673.7) mm^3; control: left = 6598.9 (682.8) mm^3, right = 6933.3 (648.4) mm^3; $F(1, 99) = 2.07$, $p = 0.15$]. There was no group by hemisphere interaction found in volume, $F(1, 99) = 0.80$, $p = 0.80$. However, there was a significant main effect for hemisphere, $F(1, 99) = 78.36$, $p < 0.0001$, with the right hemisphere exhibiting significantly larger volume than the left hemisphere. There was no significant effect of supratentorial volume $F(1, 99) = 0.05$, $p = .83$.

Thalamic Shape Comparison

Data screening revealed two subjects with values that were considered outliers based on previously defined criteria. Principal component (PC) t-tests revealed significant differences

between left and right hemisphere volumes, indicating that group comparisons were appropriate on a per hemisphere basis.

Whole thalamic shape comparison using the first 10 eigenvectors (i.e., principal components), that accounted for ~88% of the variance, showed a significant interaction of PC and group, $F(9, 91) = 5.75$, $p < .001$, Wilk's $\Lambda = 0.64$. Vertex-wise surface shape comparisons indicate inward deformation on bilateral ventral and dorsal regions, and outward deformation on left medial and left lateral regions for PPA subjects relative to controls (see Figure 1). Similar comparisons were observed for $PPA^{A\beta+}$ subjects and $PPA^{A\beta-}$ subjects relative to controls.

Correlation of Thalamic Shape and Language Scores

Mean deformation scores in each of the nuclei of interest – pulvinar, mediodorsal, anterior – were correlated against performance on select language measures – confrontation naming, syntax, repetition, and single word comprehension. Within the $PPA^{A\beta+}$ group, lower confrontation naming scores were significantly correlated with inward deformation in the left pulvinar ($r = 0.60$, $p < 0.01$), right pulvinar ($r = 0.49$, $p = 0.01$), left anterior ($r = 0.56$, $p < 0.01$), and right anterior ($r = 0.41$, $p = 0.04$; see table 4) thalamic nuclei. Lower syntax scores were significantly correlated with inward deformation in the left pulvinar ($r = 0.41$, $p = 0.04$) and left anterior ($r = 0.46$, $p = 0.02$) thalamic nuclei. Only the confrontation naming and left pulvinar and left anterior nuclei correlations survived the FDR correction (see figure 5). No significant correlations were found for the mediodorsal nucleus. No significant correlations were found for single word comprehension.

Within the $PPA^{A\beta-}$ group, there were no significant correlations between thalamic nuclei and language performance (see table 5).

Discussion

The present study sought to investigate the structural changes of the thalamus in the complex pathophysiology of non-semantic PPA. Using a carefully characterized sample of non-semantic subtyped PPA subjects, thalamic volume and shape patterns were defined based on group status and presence of underlying AD pathology. To further elucidate the relationship of thalamic pathology and language functioning, relationships between localized atrophy in specific nuclei and performance on selected language measures were then explored.

Our first aim was to investigate volumetric and shape differences between PPA and healthy controls. Our analysis revealed there was no significant differences in thalamic volume between PPA subjects and healthy controls, yet volume of the right thalamus was significantly larger than the left in both groups. The findings are inconsistent with previous literature examining thalamic volume in PPA, which suggests there is a bilateral volume decrease in PPA subjects relative to healthy individuals (Bocchetta et al., 2018). Furthermore, this work discovered that thalamic volumetric changes in PPA-related conditions, such as PPA-not otherwise specified and semantic dementia, were noted to be asymmetric, with reduced volumes in the left compared to the right thalamus (Bocchetta et al., 2018). This observation aligns with our findings in a non-semantic PPA sample of right greater than left thalamic asymmetry, regardless of neuropathology group status.

Regarding thalamic morphology, the current study found prominent abnormalities of the thalamus in PPA subjects relative to healthy control participants that occurred in the absence of volumetric differences. Inward deformation of shape parameters along the surface are representative of localized volume loss (Csernansky et al., 2004). Our findings showed a specific pattern of bilateral inward deformation in PPA subjects along the dorsal and ventral aspects of

the thalamus that extended in an anterior to posterior fashion. In addition, significant outward deformation in left medial aspects of the thalamus in PPA subjects was also observed. This is contrasted against studies of thalamic shape patterns in AD, which identified inward deformation in mediodorsal and ventral regions of the thalamus bilaterally (Zarei et al., 2009). While we also observed bilateral inward deformation in ventral regions, our findings were not supportive of inward deformation, but rather outward deflections of mediodorsal regions. This suggests the presentation of AD pathology and its relationship to thalamic integrity may differ as a function of the clinical presentations between various neurodegenerative disorders. The finding has several implications for the study of AD pathology and its effects on critical brain structures as well as its influence on cognition. Future studies should investigate further the relationship of these changes with changes present in other regions (i.e., cortical regions critical in language functioning).

Our second aim examined the influence of underlying neuropathology in PPA on thalamic morphology. Current literature suggests approximately 30% of PPA subjects have suspected AD pathology (Mesulam et al., 2008; Knibb et al., 2005), despite the presentation of similar clinical deficits. Our hypothesis that PPA$^{A\beta+}$ subjects would demonstrate significantly greater thalamic deformation compared to PPA $^{A\beta-}$ subjects was unsupported. Specifically, we observed no statistical difference in thalamic shape or volume for PPA $^{A\beta+}$ subjects relative to PPA$^{A\beta-}$. Similarly, a previous study showed that thalamic volume alone could not discriminate among different forms of FTD of varying underlying pathologies (Bocchetta et al., 2018). Findings suggest that the underlying pathological processes involved in PPA do not differentially impact the integrity of the thalamus.

Finally, we sought to determine how deformation patterns in relevant thalamic nuclei – pulvinar, mediodorsal, anterior - relate to performance on language tasks measuring confrontation naming, syntax, single word comprehension, and repetition. These aspects of language were investigated because they reflect the main deficits in PPA. Overall, it was found that shape patterns in thalamic nuclei related to language deficits in $PPA^{A\beta+}$ subjects alone. Significant positive relationships between confrontation naming with bilateral pulvinar and anterior nuclei were noted in $PPA^{A\beta+}$, such that a poorer confrontation naming performance was related to greater inward deformation, or localized volume loss. There was also a significant positive correlation for syntax with left pulvinar and anterior nuclei in $PPA^{A\beta+}$ subjects, such that poor performance for syntax was related to increased inward deformation. Finally, repetition was significantly positively correlated to deformation in the left anterior nucleus, such that a poorer performance for repetition was related to greater inward deformation. No relationships were found between the mediodorsal nucleus and language measures, as well as single word comprehension with thalamic nuclei. After correcting for multiple comparisons, only the relationship between confrontation naming and the left pulvinar and left anterior nuclei were significant for $PPA^{A\beta+}$ subjects.

In the context of $PPA^{A\beta+}$, studies reveal these individuals tend to exhibit greater memory, visuospatial, and executive impairments relative to other PPA subjects (Bergeron et al., 2018). This is consistent with our finding that only subjects with suspected AD pathology showed structural changes as they relate to performance on language measures. However, despite the similar structural changes in $PPA^{A\beta+}$ and $PPA^{A\beta-}$ subjects, the effect of the shape changes on language performance (confrontation naming, single word comprehension, and syntax) depended upon underlying pathology. The reason for this is unclear and should be explored further. Post-

mortem analyses will be conducted to verify underlying pathology and provide foundation for further research.

Furthermore, our findings are consistent with the extensive literature describing aphasia syndromes that result from thalamic stroke. These studies indicate that lesions to any one of the mediodorsal, pulvinar, or anterior nuclei may produce naming and speech deficits, although some differentiation has also been shown between the pulvinar and anterior nuclei, producing non-fluent aphasia and fluent aphasia, respectively (Maeshima & Osawa, 2018). The current study demonstrated further support for the role of these nuclei in language and evidence that there may be a role of the thalamus in the neurodegenerative disorder characterized by aphasia. The current study revealed a strong relationship between shape deformation of thalamic nuclei with confrontation naming, specifically, in individuals with underlying AD pathology. The mechanism underlying these differences should be explored in future studies. Given that the relationships between language performance and shape patterns in thalamic nuclei were different depending upon the presence or absence of AD pathology, future studies should focus on the impact of pathology and its role in differentiating different types of PPA.

Limitations for the current study include aspects related to the methodology. Inherent with morphology research, inward/outward deformation does not necessarily indicate loss/gain of function, which can be informed with correlational approaches, but no causal claims can be made. Additionally, there is always some inherent error using automated imaging systems. 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 may be present. However, this type of error is minimized due to consistency across images. Finally, despite the large sample size for the unique population and the sensitivity

analyses supporting our conclusions, it is possible that findings would be more accurate with more subjects.

Future directions for this work include investigating thalamic changes that occur due to AD in the thalamus to understand the differential effects of underlying pathology on structure – language relationships despite similar clinical presentations. In addition, future studies would benefit from integration of cortical findings in order to provide a more robust picture of pathophysiology regarding AD pathology in non-semantic PPA individuals. Overall, the current study is the first to investigate thalamic integrity, as measured by shape deformation, in PPA. Its findings reveal significant dorsal, ventral, and medial abnormalities of the thalamus in PPA relative to healthy individuals. Furthermore, language functioning in $PPA^{A\beta+}$ subjects appears particularly susceptible to these changes.

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Table 1. Subject Characteristics by Group

		PPA, n = 57	Control, n = 44
F/M (% female)		22/35 (39)	19/25 (43)
Mean (SD) age in years		66.7 (7.2)	64.2 (6.4)
Mean (SD) education in years		16.2 (2.4)	15.9 (2.3)
WAB Aphasia Quotient	Mean (SD)	84.6 (11.1)	99.8 (0.6)
	Range	41.8-97.1	98-100

Abbreviations: WAB, Western Aphasia Battery

Table 2. Subject Characteristics by Pathology

		$PPA^{A\beta+}$, n = 31	$PPA^{A\beta-}$, n = 26
F/M (% female)		22/35 (71)	12/19 (46)
Mean (SD) age in years		66.7 (7.2)	66.39 (6.3)
Mean (SD) education in years		16.2 (2.4)	16.66 (2.3)
WAB Aphasia Quotient	Mean (SD)	84.03 (10.38)	85.31 (12.17)
	Range	63.90-97.10	41.80-97.00

Abbreviations: WAB, Western Aphasia Battery

Table 3. Neuropsychological Measures

		Group		**Pathology**	
		PPA, n = 57	Control, n = 44	$PPA^{A\beta+}$, n = 31	$PPA^{A\beta-}$, n = 26
WAB AQ	Mean (SD)	84.61 (11.13)	-	84.03 (10.38)	85.31 (12.17)
	Range	41.80-97.10	98-100	63.90-97.10	41.80-97.00
BNT	Mean (SD)	42.88 (15.22)**	58.60 (1.40)**	39.32 (14.95)*	47.22 (14.72)*
	Range	6-59	55-60	6-58	9-59
PPVT	Mean (SD)	33.59 (2.92)**	35.51 (0.66)**	33.68 (2.11)	33.48 (3.73)
	Range	18-36	34-36	29-36	18-36
NAT Total	Mean (SD)	22.57 (6.33)**	29.66 (0.76)**	23.29 (5.21)	21.70 (7.50)
	Range	3-30	27-30	6-30	3-30
WAB Rep	Mean (SD)	80.94 (13.08)**	99.29 (1.23)**	78.21 (12.61)	84.26 (13.13)
	Range	42-98	95-100	51-98	42-98

Abbreviations: WAB AQ = Western Aphasia Battery- Aphasia Quotient; BNT = Boston naming test; PPVT = Peabody Picture Verbal Test; NAT = Northwestern Anagram Test; WAB Rep = Western Aphasia Battery- Repetition

** $p < 0.001$, * $p < 0.05$

Table 4. Correlations Between Neuropsychological Measure and Thalamic Nuclei for $PPA^{A\beta+}$ subjects by Hemisphere

	BNT	PPVT	NAT	WAB Rep
L Pulvinar	0.60**	0.22	0.41*	0.25
L Mediodorsal	0.27	0.10	0.09	-0.10
L Anterior	0.56**	0.19	0.46*	0.24
R Pulvinar	0.49*	0.13	0.14	-0.02
R Mediodorsal	0.15	-0.03	-0.08	-0.22
R Anterior	0.42*	0.10	0.22	0.00

Abbreviations: BNT: Boston Naming Test, PPVT: Peabody Picture Verbal Test, NAT: Northwestern Anagram Test, WAB Rep: Western Aphasia Battery – repetition subtest

*$p < 0.05$, **$p < 0.01$

Table 5. Correlations Between Neuropsychological Measure and Thalamic Nuclei for $PPA^{A\beta-}$ subjects by Hemisphere

	BNT	PPVT	NAT	WAB Rep
L Pulvinar	0.01	0.06	-0.02	0.02
L Mediodorsal	0.01	0.18	-0.05	-0.21
L Anterior	0.02	-0.06	-0.02	0.02
R Pulvinar	-0.12	-0.08	-0.09	-0.01
R Mediodorsal	0.19	0.25	-0.01	-0.02
R Anterior	-0.21	-0.12	-0.11	-0.11

Abbreviations: BNT: Boston Naming Test, PPVT: Peabody Picture Verbal Test, NAT: Northwestern Anagram Test, WAB Rep: Western Aphasia Battery – repetition subtest

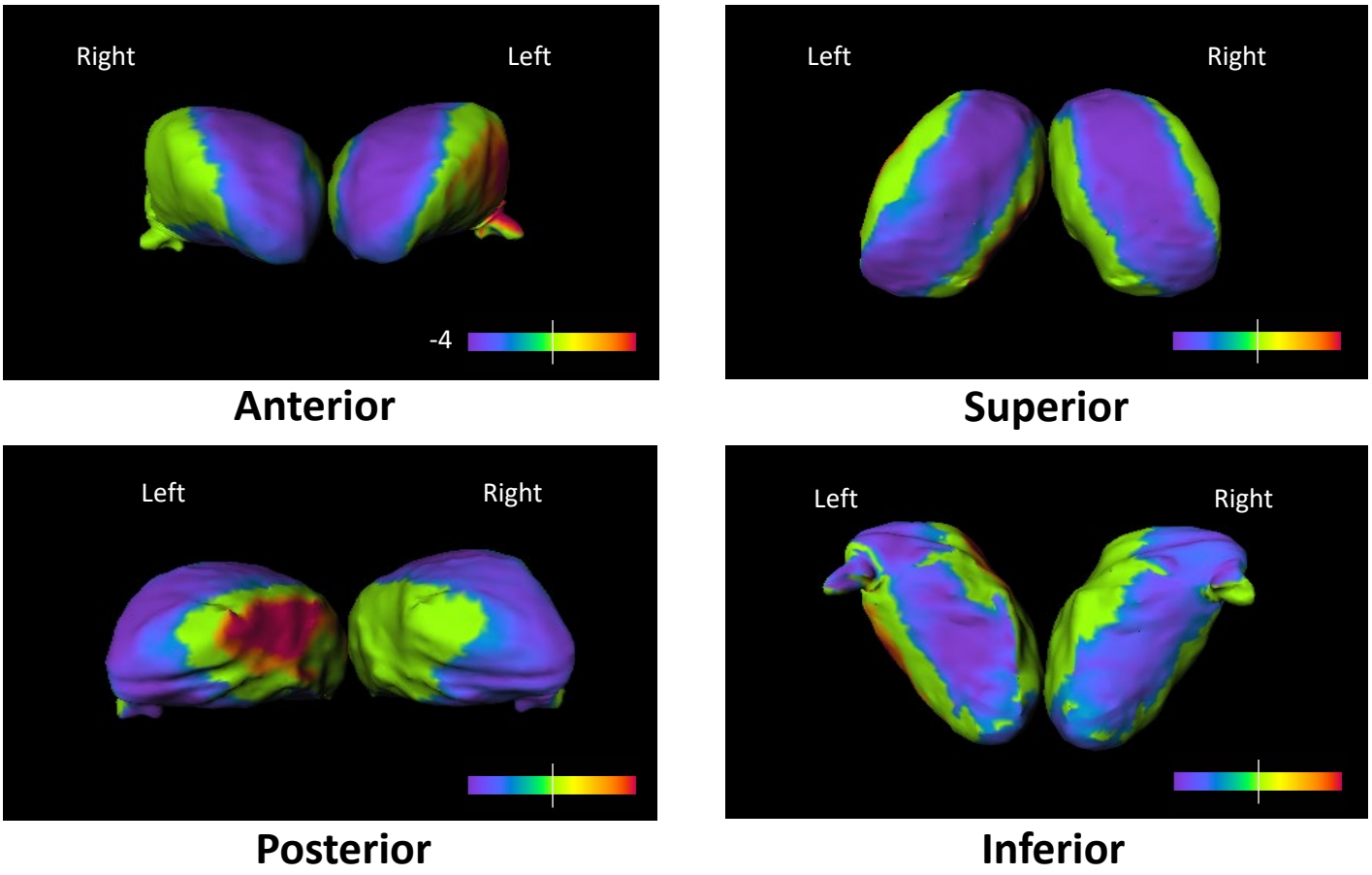

Figure 1. CON vs PPA. Shape comparison between PPA vs. control subjects. Cooler shades (blue) represent greater inward deformation of the PPA group relative to controls. Warmer shades (red) represent greater outward deformation of the PPA group relative to controls. Note: RFT was applied to account for multiple comparisons.

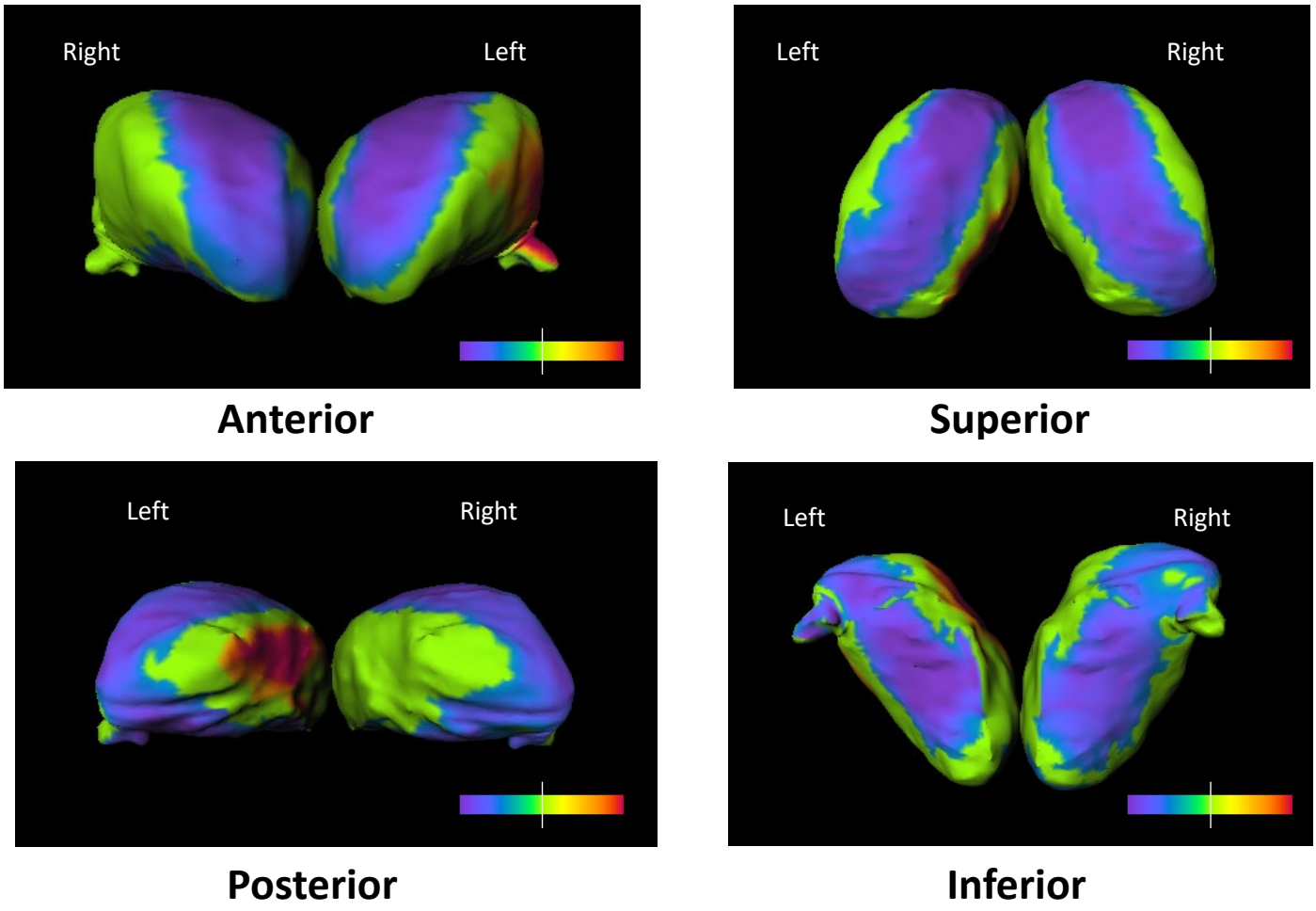

Figure 2. CON vs PPA$^{A\beta+}$. Shape comparison between PPA$^{A\beta+}$ subjects vs. control subjects. Cooler shades (blue) represent greater inward deformation of PPA$^{A\beta+}$ subjects relative to controls. Warmer shades (red) represent greater outward deformation of PPA$^{A\beta+}$ subjects relative to controls. Note: RFT was applied to account for multiple comparisons.

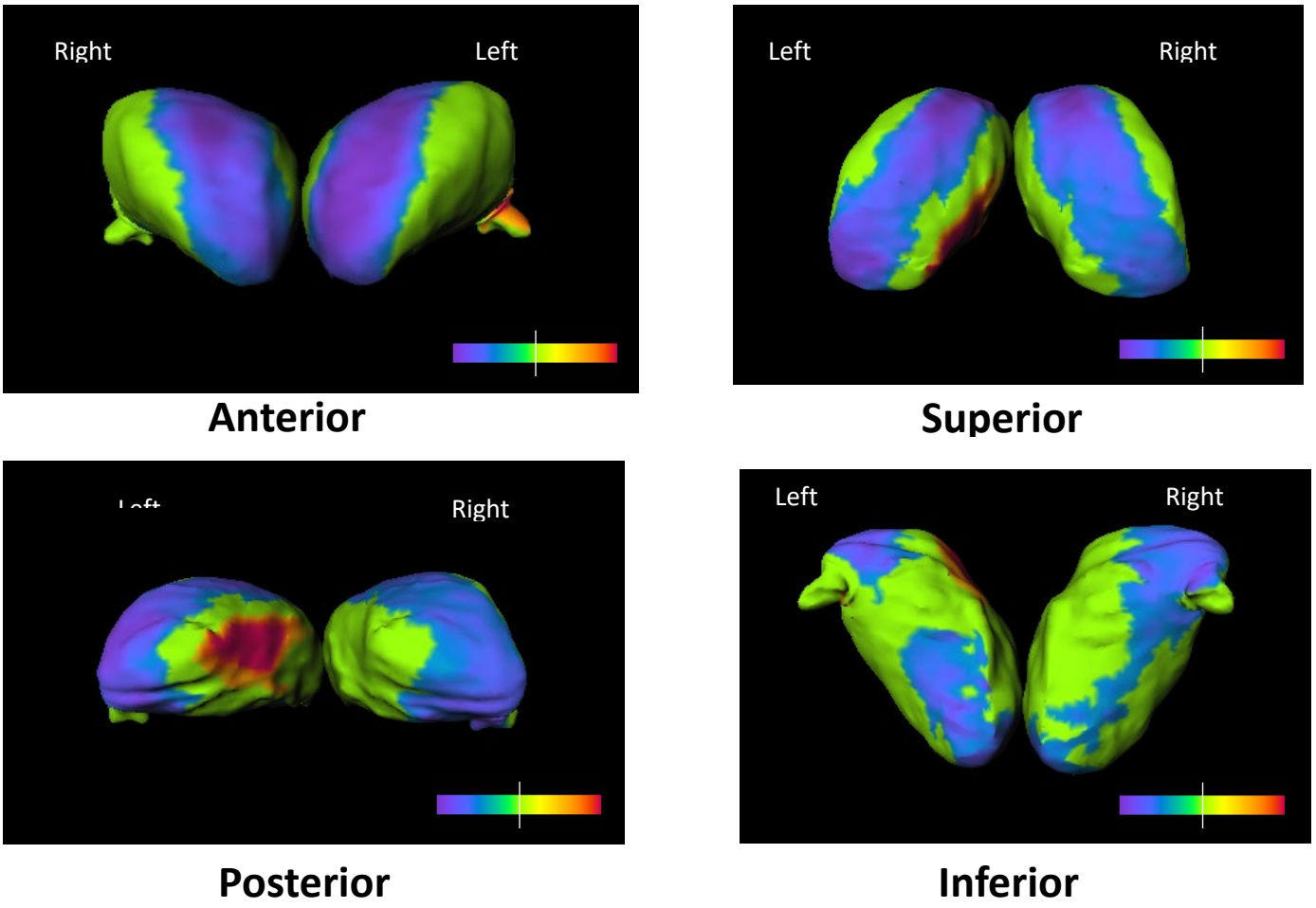

Figure 3. CON vs PPA$^{A\beta-}$. Shape comparison between PPA$^{A\beta-}$ subjects vs. control subjects. Cooler shades (blue) represent greater inward deformation of PPA$^{A\beta-}$ subjects relative to controls. Warmer shades (red) represent greater outward deformation of PPA$^{A\beta-}$ subjects relative to controls. Note: RFT was applied to account for multiple comparisons.

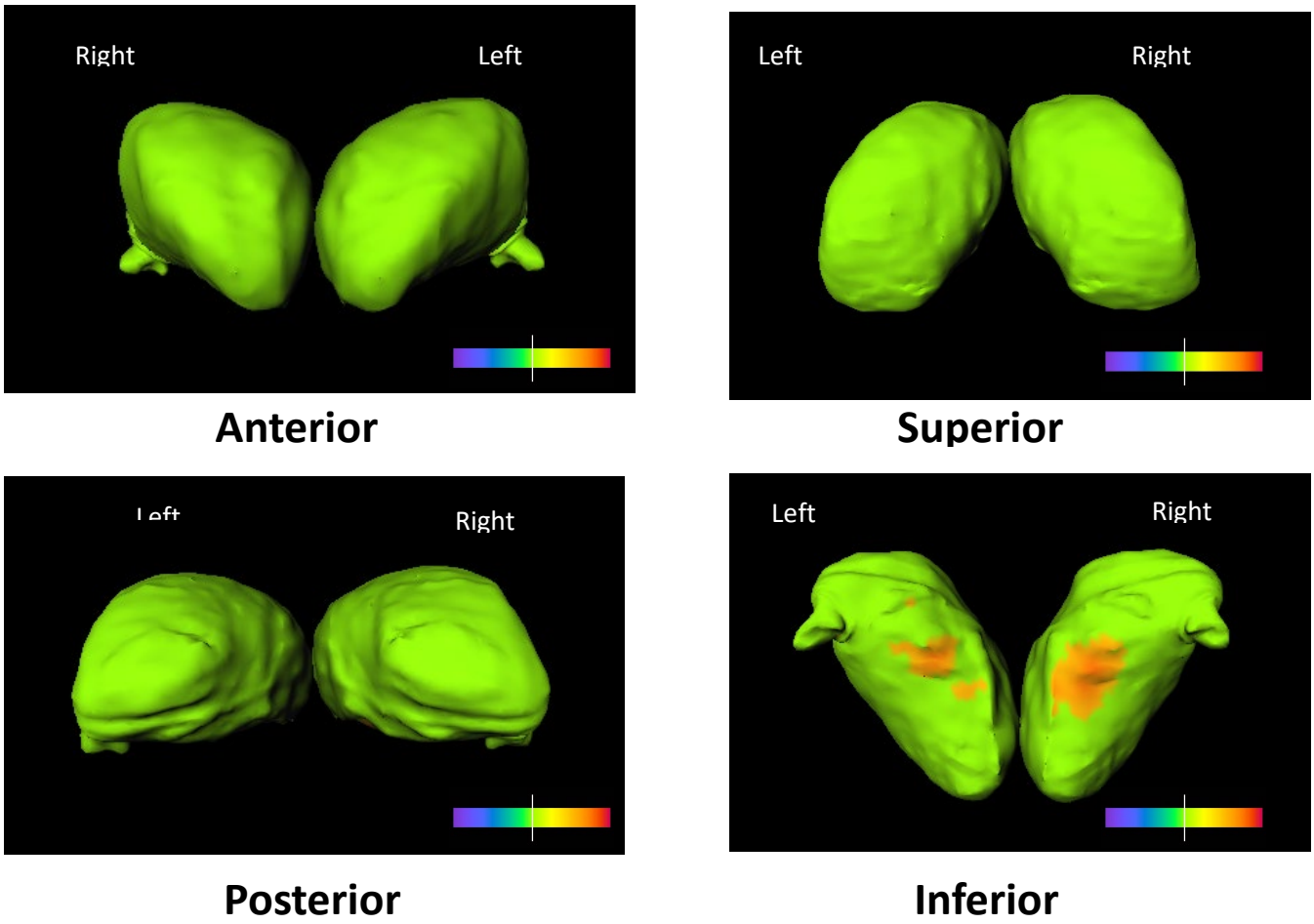

Figure 4. $PPA^{A\beta+}$ vs $PPA^{A\beta-}$. Shape comparison between $PPA^{A\beta+}$ subjects vs. $PPA^{A\beta}$ subjects. Cooler shades (blue) represent greater inward deformation of $PPA^{A\beta+}$ subjects relative to the $PPA^{A\beta}$ subjects. Warmer shades (red) represent greater outward deformation of $PPA^{A\beta+}$ subjects relative to $PPA^{A\beta}$ subjects. Note: RFT was applied to account for multiple comparisons.

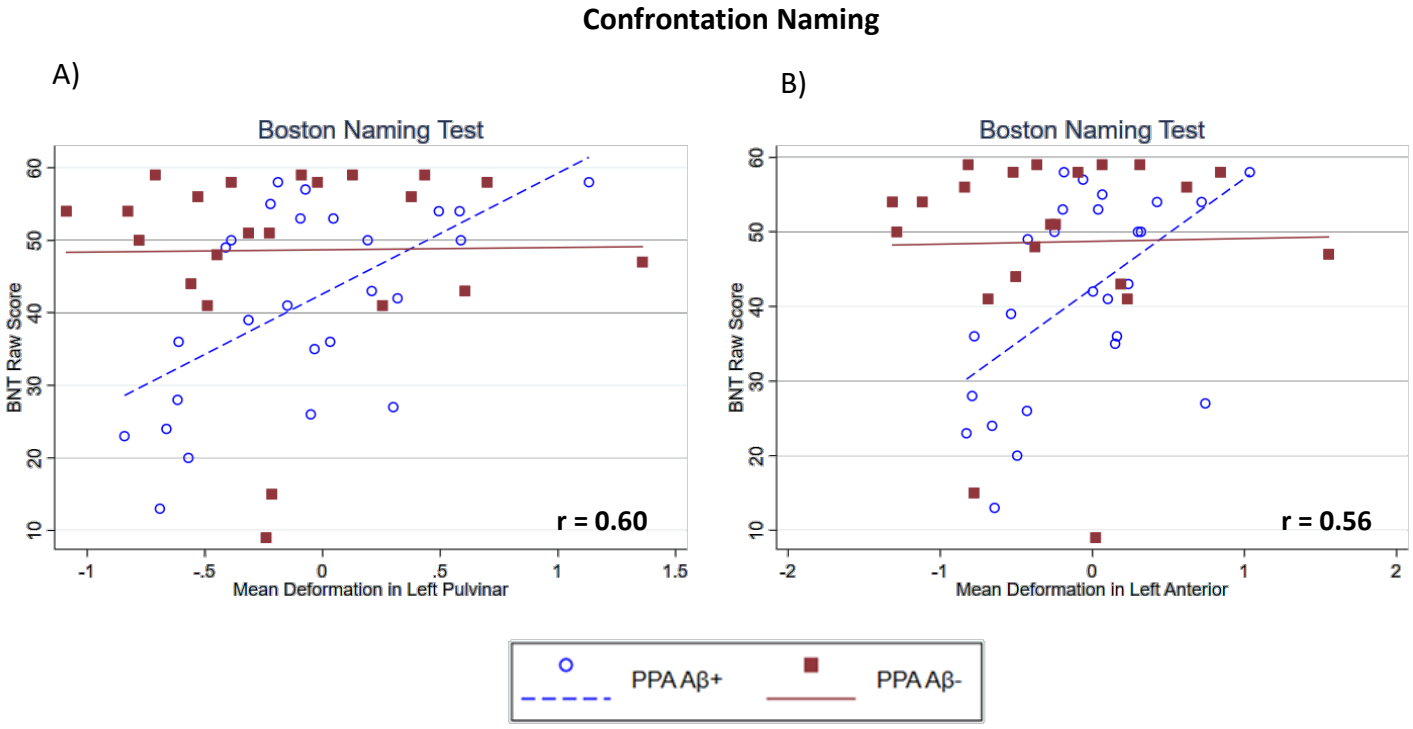

Figure 5. Correlation between thalamic shape scores and language performance within the PPA group that survived FDR correction. Higher BNT scores indicate a greater performance on confrontation naming. Shape scores that are more positive represent outward deformation relative to healthy controls whereas more negative scores represent inward deformation relative to healthy controls. Red scores represent $PPA^{A\beta-}$ subjects whereas blue scores represent $PPA^{A\beta+}$ subjects. A) Correlation between thalamic shape scores in the left pulvinar nucleus and BNT raw score. B) Correlation between thalamic shape scores in the left anterior nucleus and BNT raw score. Abbreviations: BNT = Boston Naming Test.