

RESEARCH ARTICLE

# Longitudinal naming and repetition relates to AD pathology and burden in autopsy-confirmed primary progressive aphasia

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## Abstract

**Introduction:** In primary progressive aphasia (PPA) patients with autopsy-confirmed Alzheimer's disease (AD) or frontotemporal lobar degeneration (FTLD), we tested how the core clinical features of logopenic PPA—naming and repetition—change over time and relate to pathologic burden.

**Methods:** In PPA with AD (n = 13) or FTLD (n = 16) pathology, Boston Naming Test and Forward Digit Span measured longitudinal naming and repetition; as reference, Mini-Mental State Examination (MMSE) measured global cognition. Pathologic burden in left peri-Sylvian regions was related to longitudinal cognitive decline.

**Results:** PPA with AD showed greater decline in naming ( $P = 0.021$ ) and repetition ( $P = 0.020$ ), compared to FTLD; there was no difference in MMSE decline ( $P = 0.99$ ). Across all PPA, declining naming ( $P = 0.0084$ ) and repetition ( $P = 0.011$ ) were associated with angular, superior-middle temporal (naming  $P = 0.014$ ; repetition  $P = 0.011$ ) and middle frontal (naming  $P = 0.041$ ; repetition  $P = 0.030$ ) pathologic burden.

**Discussion:** Unique longitudinal profiles of naming and repetition performance in PPA with AD are related to left peri-Sylvian pathology.

## KEYWORDS

Alzheimer's disease, frontotemporal lobar degeneration, primary progressive aphasia

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## 1 | INTRODUCTION

Primary progressive aphasia (PPA) is a neurodegenerative condition characterized by progressive language impairment, typically in the first 2 years of disease onset.<sup>1</sup> Three clinical variants of PPA have been described through consensus criteria.<sup>2</sup> Non-fluent/agrammatic PPA (naPPA) is marked by slow, agrammatic speech and speech errors; semantic variant PPA (svPPA) is characterized by poor semantic knowledge. Finally, lexical retrieval and the phonological loop are impaired in logopenic variant PPA (lvPPA) due to left peri-Sylvian disease, leading to naming difficulty and reduced repetition.<sup>3-6</sup> Importantly, each variant is statistically associated with different underlying pathologic etiologies:<sup>7-9</sup> naPPA and svPPA syndromes are associated with frontotemporal lobar degeneration (FTLD) spectrum pathology, while lvPPA is frequently associated with Alzheimer's disease (AD) neuropathology.<sup>10-12</sup> Even so, the high degree of clinical heterogeneity<sup>13-17</sup> can make discrimination between variants inconsistent. In addition, there is evidence that some cerebrospinal fluid (CSF) biomarkers are less sensitive to non-amnesic forms of AD, such as lvPPA,<sup>18</sup> thereby reducing discrimination of AD from FTLD during life. In this context, it is critical to identify objective clinical screening markers that are pathologically specific and can support biological markers. Because clinical features depend on disease severity, it is equally essential to characterize how these clinical markers change over disease course in PPA and relate to neuropathologic burden.

If one goal of language-specific characterization is to support in vivo discrimination of pathologic etiology in PPA, clinical studies must examine gold standard, autopsy-confirmed cases. We can further enhance our understanding of the neurobiology of language by relating specific language features during life to pathology in a specific anatomic distribution.<sup>19,20</sup> While the broad pathology, the laterality, and anatomic distribution of pathology have been examined previously in PPA syndromes,<sup>9,13,11,21</sup> studies relating regional pathologic burden to specific, *ante mortem* language features are very rare. To this end, our group previously found that repetition, measured by Forward Digit Span, is selectively impaired in PPA patients with underlying AD pathology, compared to FTLD.<sup>12</sup>

Here, we expand on previous work by longitudinally evaluating the two core language features of lvPPA<sup>2</sup>—impaired repetition and confrontation naming—to directly compare how impairment changes over disease course in PPA with AD compared to FTLD pathology. Naming and repetition performance were tracked using the Boston Naming Test (BNT) and Forward Digit Span, respectively. To ensure specificity of decline, Mini-Mental State Examination (MMSE) tracked global cognitive decline. It is important to note that naming difficulty is a ubiquitous feature of PPA, due in part to disease in several neural substrates thought to contribute to naming.<sup>12,22</sup> Even so, different underlying proteinopathies in PPA may have diverging longitudinal naming and repetition profiles: svPPA presents with severe naming deficits early in disease course, due in part to anterior temporal lobe atrophy, while naPPA shows persistently mild-to-moderate naming impairments throughout disease, related in part to lateral and inferior

### RESEARCH IN CONTEXT

- 1. Systematic review:** Literature was reviewed using PubMed and Google Scholar. The pathological etiology of primary progressive aphasia (PPA) is heterogeneous: while PPA is often associated with frontotemporal lobar dementia (FTLD) pathology, logopenic PPA may be indicative of Alzheimer's disease (AD) pathology. However, clinical diagnoses can be subjective and many PPA patients do not fit into classic syndromic categories. Autopsy studies relating specific clinical features of PPA to *post mortem* pathology are still needed.
- 2. Interpretation:** We tested two core features of logopenic PPA that may indicate AD pathology: impaired naming (Boston Naming Test) and repetition (Forward Digit Span). Findings reveal that longitudinal decline in naming and repetition is associated with AD pathology and higher pathological burden in peri-Sylvian regions.
- 3. Future directions:** Naming and repetition may be clinical markers of AD in PPA that can be used to track disease progression. Future studies should explore how these clinical features relate to biofluid markers of underlying pathology in PPA.

### HIGHLIGHT

- Different variants of PPA associate with distinct AD vs. FTLD pathologies
- Longitudinal BNT and forward digit span assess naming and repetition, respectively
- Greater decline in naming and repetition in PPA with AD pathology, compared to FTLD
- No difference in global cognitive decline was observed across AD and FTLD
- Declines in naming and repetition are associated with peri-Sylvian pathology burden

frontal atrophy,<sup>1,23,24</sup> and both naPPA and svPPA show relatively preserved repetition.<sup>4,12</sup> We therefore hypothesize that AD PPA patients may exhibit progressive naming and repetition decline, due in part to spreading disease in peri-Sylvian regions.<sup>3</sup> By contrast, we expect FTLD PPA to show only mild repetition difficulty, and sustained naming difficulty throughout disease. Finally, we test how *ante mortem* longitudinal performance in naming and repetition relate to pathologic burden in peri-Sylvian language regions associated with lexical retrieval<sup>24-26</sup> and the phonological loop:<sup>27,28</sup> superior-middle temporal (SMT) gyrus, angular (ANG) gyrus, and middle-inferior frontal (MF) gyrus. As a reference region minimally involved in these

language features, we also related longitudinal performance to pathology in the occipital cortex (OC). We hypothesized that accumulating pathology in peri-Sylvian loci in PPA patients would be associated with declining naming and repetition performance over the disease course.

## 2 | METHODS

### 2.1 | Participants

In this retrospective study, 29 participants were selected from the University of Pennsylvania (Penn) Integrated Neurodegenerative Disease Database (INDD)<sup>29</sup> and autopsied at the Center for Neurodegenerative Disease Research (CNDR). Inclusion criteria were a clinical diagnosis of PPA, *ante mortem* longitudinal forward span and/or BNT data (two or more timepoints), and a pathological diagnosis of AD (n = 13) or FTLD (n = 16) at autopsy. All participants and legally responsible next of kin completed written informed consent for the neuropsychological testing and subsequent autopsy protocols using a protocol approved by Penn's Institutional Review Board.

Clinical diagnoses of svPPA (n = 11), naPPA (n = 5), or lvPPA (n = 13) were made by the patient's primary cognitive neurologist (MG, DJJ) using PPA criteria<sup>2</sup> through multidisciplinary consensus meetings at the Penn Frontotemporal Degeneration Center (FTDC). Patients reported English as their primary language. We previously reported repetition<sup>12</sup> and pathology diagnosis<sup>12,23</sup> for a subset of these patients.

### 2.2 | Neuropathological assessment

Fresh tissue from a single hemisphere was sampled at autopsy in standardized regions for diagnosis and fixed overnight in 10% neutral buffered formalin.<sup>30</sup> Tissue was processed and embedded in paraffin blocks and cut into 6  $\mu$ m sections for immunohistochemical staining for tau, amyloid beta (A $\beta$ ), TAR DNA-binding protein 43 (TDP-43), and alpha-synuclein with well-characterized antibodies as described.<sup>31</sup>

#### 2.2.1 | Pathological criteria

Neuropathological diagnosis of AD was determined by criteria for "high" AD neuropathologic change (ADNC; n = 13).<sup>32</sup> FTLD pathology was classified by current neuropathological criteria defined by accumulations of misfolded tau (FTLD-tau; n = 6) or transactive response DNA-binding protein of 43 kDa (TDP-43; FTLD-TDP; n = 10).<sup>33</sup> Exclusion criteria were co-occurring vascular disease. FTLD patients had negligible co-occurring pathologies (none or low ADNC). A majority of AD patients (10 of 13) had one or more co-occurring pathologies at autopsy, typical of AD:<sup>34</sup> cerebral amyloid angiopathy (n = 1), limbic-predominate age-related TDP-43 encephalopathy (n = 6), and/or  $\alpha$ -synuclein (n = 8).

### 2.2.2 | Regional pathology burden scores

Pathology burden for each region of interest (ROI) was assessed prospectively at the time of neuropathological diagnosis.<sup>32</sup> We focus on three core left peri-Sylvian ROIs thought to contribute to naming and repetition:<sup>24,26–28</sup> SMT, ANG, and MF. While additional regions are implicated in naming and repetition, these ROIs were reliably sampled at autopsy according to standard criteria.<sup>32</sup> In addition, OC pathologic burden was assessed as a reference control region; OC ordinal scores were missing for 11 patients. Each ROI was scored for pathological severity based on pathologists' expert judgment (JQT, EBL) at time of autopsy, and was graded on an ordinal 0- to 3-point scale (i.e., 0 = none, 0.5 = rare, 1 = low, 2 = intermediate, 3 = high) according to criteria.<sup>32</sup> We focused on brain samples from the left hemisphere, due to known laterality of histopathology in PPA to left-hemisphere language regions;<sup>11,23</sup> and excluded seven patients (two AD) with sampling only from the right hemisphere. Burden was determined based on primary proteinopathy in each group: tau pathology in AD and FTLD-tau, and TDP-43 in FTLD-TDP. Because amyloid is less related to cognitive deficits than tau in AD,<sup>35</sup> amyloid scores were not included in the pathologic burden measure for AD.

### 2.3 | Neuropsychological testing

#### 2.3.1 | Lexical retrieval

The BNT is an object-naming assessment in which line-drawn images are presented for oral identification. This was completed at least twice, with testing sessions at least 6 months apart. We used two adapted versions of the BNT to account for legacy data in our cohort: a 15-item version used in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD),<sup>36</sup> and a 30-item version including odd items from the original 60-item BNT.<sup>37</sup> Performance was calculated as percent correct. Patients had a median of three testing sessions (interquartile range [IQR] = 2).

#### 2.3.2 | Repetition

Forward Span is the maximum sequence of digits a patient can repeat in forward order.<sup>38</sup> Longitudinal Forward Span was available for a subset of patients (12 AD, 11 FTLD), and patients had a median of three testing sessions (IQR = 1.5).

#### 2.3.3 | Global cognition

MMSE is an assessment of global cognition, including orientation, attention, memory, language, and visuospatial functioning domains.<sup>39</sup> The majority of MMSE (88 of 91 timepoints) were collected on the same day as BNT (median interval = 0 days, IQR = 0, max interval = 7.9 months). MMSE was unavailable for four timepoints.

## 2.4 | Statistical analyses

Non-parametric Mann-Whitney-Wilcoxon and Chi-square tests compared demographic, baseline clinical, and pathological characteristics across AD and FTLD. An exploratory analysis of FTLD subtypes (FTLD-tau, FTLD-TDP) is included in the supporting information.

Linear mixed effects models tested naming and repetition performance in PPA over disease duration to determine whether rate of decline differed by pathology (AD, FTLD). BNT % correct and maximum Forward Span were tested as dependent variables; disease duration from symptom onset to testing session (years), pathology group (AD, FTLD), clinical phenotype, and the interaction between disease duration and pathology were included as fixed effects, as well as age at death (years), sex, and years of education; individual was included as a random intercept (Equations 1, 2). Analysis of Deviance Tables (Type II Wald chi-square tests) report results. Education was missing and imputed for one AD patient based on AD group mean. To ensure that differences in decline between AD and FTLD are specific to naming and repetition, we also tested how global cognition changed over time across pathology (Equation 3). Marginal  $r^2$  described variance explained by fixed effects. Because age at death,<sup>40</sup> education,<sup>41</sup> and sex<sup>42</sup> can affect cognitive performance or pathology accumulation, we included each of these variables in our mixed effects models. To ensure robustness of our findings, we repeated models excluding these factors; importantly, none of the main findings changed when sex, age, and education were not included (results not shown).

$$\begin{aligned} \text{BNT} \sim & \text{Pathology} * \text{Disease Duration} + \text{Phenotype} + \text{Age at Death} \\ & + \text{Sex} + \text{Education} + (1|\text{Individual}) \end{aligned} \quad (1)$$

$$\begin{aligned} \text{Forward Span} \sim & \text{Pathology} * \text{Disease Duration} + \text{Phenotype} \\ & + \text{Age at Death} + \text{Sex} + \text{Education} + (1|\text{Individual}) \end{aligned} \quad (2)$$

$$\begin{aligned} \text{MMSE} \sim & \text{Pathology} * \text{Disease Duration} + \text{Phenotype} + \text{Age at Death} \\ & + \text{Sex} + \text{Education} + (1|\text{Individual}) \end{aligned} \quad (3)$$

To confirm significant interactions between decline and pathology, analyses of variance (ANOVA) compared goodness of fit of interaction models (Equations 1, 2) to null models with no interaction between decline and pathology group (Equations 4, 5); Akaike information criterion (AIC), Bayesian information criterion (BIC), and log likelihood were reported.

$$\begin{aligned} \text{BNT} \sim & \text{Pathology} + \text{Disease Duration} + \text{Phenotype} + \text{Age at Death} \\ & + \text{Sex} + \text{Education} + (1|\text{Individual}) \end{aligned} \quad (4)$$

$$\begin{aligned} \text{Forward Span} \sim & \text{Pathology} + \text{Disease Duration} + \text{Phenotype} \\ & + \text{Age at Death} + \text{Sex} + \text{Education} + (1|\text{Individual}) \end{aligned} \quad (5)$$

Next, we tested how individual rate of BNT and Forward Span decline related to pathology burden in ROIs: left SMT, left ANG, and left MF. Left OC was tested as a reference control region. Individualized slopes of BNT and Forward Span decline were calculated from mixed effects models. Severity of pathology burden was scored (0–3) according to primary proteinopathy: tau pathology in AD and FTLD-tau, and TDP-43 in FTLD-TDP. Across all patients, non-parametric Spearman correlations tested associations of individualized slope of decline with ROI pathological burden.

Analyses were conducted in the R statistical environment using linear mixed effects (lme4),<sup>43</sup> multi-model inference (MuMIn),<sup>44</sup> and companion to applied regression (car)<sup>45</sup> packages.

## 3 | RESULTS

### 3.1 | Demographic and pathologic characteristics

AD and FTLD patients did not differ in age-related variables, survival (years from onset to death), education, or sex distribution. Nor did they differ in number of testing sessions (BNT, Digits). Patients with AD pathology were more frequently clinically diagnosed with lvPPA than FTLD patients, consistent with previous reports.<sup>9</sup>

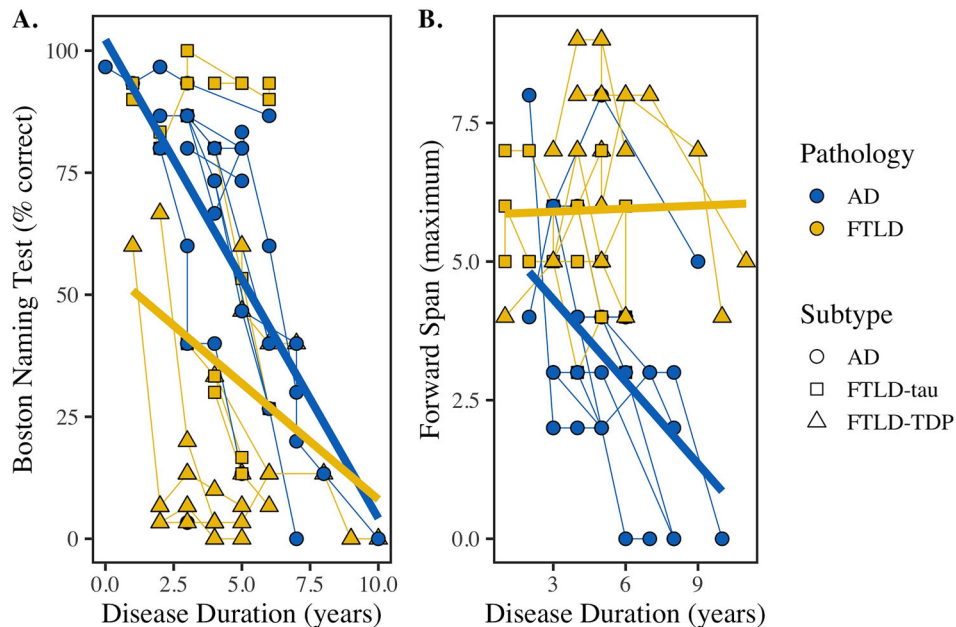
### 3.2 | Longitudinal confrontation naming (BNT) and repetition (Forward Span)

At baseline, PPA with AD had shorter Forward Span ( $W = 23, P = 0.008$ ) than FTLD, while FTLD had worse BNT than AD ( $W = 149.5, P = 0.047$ ); there was no difference between AD and FTLD on MMSE at baseline ( $W = 68, P = 0.27$ ). We next tested longitudinal BNT and Forward Span performance, and if rate of decline differed by pathology (Figure 1A,B). Mixed effects models showed that BNT significantly declined over time, and this decline was greater in AD than FTLD (marginal  $r^2 = 0.68$ ; Table 1); Forward Span also decreased over time, and was greater in AD than FTLD (marginal  $r^2 = 0.52$ ; Table 1). While MMSE also declined significantly over time, there was no significant interaction with pathology, indicating similar rates of decline between AD and FTLD (marginal  $r^2 = 0.51$ ; Table 1).

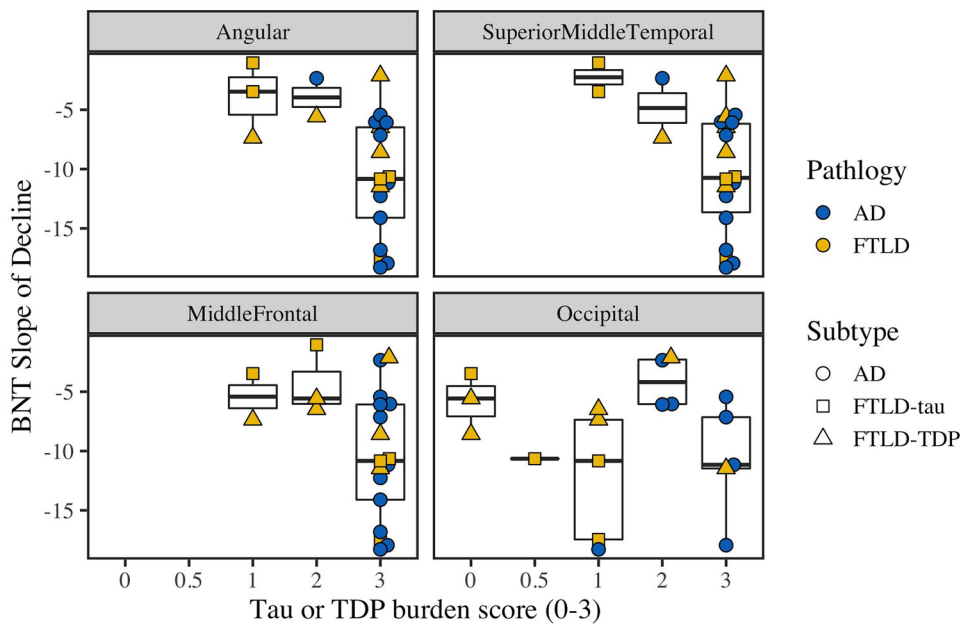
ANOVAs showed that BNT (Table 2A) and Forward Span (Table 2B) models with an interaction term had significantly better fit than null models without an interaction, further confirming that AD patients declined faster than FTLD.

### 3.3 | Regional clinical–pathological associations

Mann-Whitney-Wilcoxon tests compared ordinal pathologic severity scores in each ROI between AD and FTLD (Table 3). Spearman correlations tested the relationship between pathological burden in left perisylvian ROIs and rate of decline during life. Across all PPA patients, BNT decline was significantly associated with degree of pathological burden (Figure 2) in ANG ( $\rho = -0.55, P = 0.0084$ ), SMT ( $\rho = -0.51,$



**FIGURE 1** A, Boston Naming Test (BNT) and (B) Forward Span over time in primary progressive aphasia (PPA) patients with Alzheimer's disease (AD) or frontotemporal lobar dementia (FTLD). Spaghetti plots showing comparisons of longitudinal BNT performance and Forward Span performance across AD (blue) and FTLD (yellow) PPA patients. Shape indicates pathological subtype (AD, FTLD-tau, FTLD-TAR DNA-binding protein)



**FIGURE 2** Boston Naming Test (BNT) decline related to pathologic severity in primary progressive aphasia (PPA) patients with Alzheimer's disease (AD) or frontotemporal lobar dementia (FTLD). Individual rate of decline in BNT by pathological (tau or TAR DNA-binding protein [TDP]) accumulation. Color indicates pathology (AD, FTLD) of PPA patients. Shape indicates pathological subtype (AD, FTLD-tau, FTLD-TDP)

$P = 0.014$ ) and MF ( $\rho = -0.44, P = 0.041$ ); there was no association in the OC control region ( $\rho = -0.09, P = 0.71$ ). Likewise, Forward Span decline (Figure 3) was significantly associated with ANG ( $\rho = -0.57, P = 0.011$ ), MF ( $\rho = -0.5, P = 0.030$ ), and SMT pathological burden ( $\rho = -0.57, P = 0.011$ ); there was no association with OC pathological burden ( $\rho = -0.22, P = 0.42$ ).

#### 4 | DISCUSSION

Each variant of PPA is statistically associated with distinct etiologies, with lvPPA being most commonly associated with AD neuropathology. Even so, clinical and neuroanatomic delineations between PPA syndromes can be muddled,<sup>13,46,47</sup> and it is critical to identify specific



**TABLE 1** Demographic, autopsy, and baseline cognitive data for PPA patients

	AD	FTLD	P
n	13	16	
Age at onset (years)	62.0 [55.0, 67.0]	60.0 [54.8, 63.0]	.468
Age at death (years)	72.0 [64.0, 76.0]	68.0 [63.8, 72.2]	.272
Survival (years)	10.0 [9.0, 12.0]	9.0 [6.0, 10.2]	.184
Education (years)	16.0 [13.5, 16.0]	14.0 [12.0, 17.2]	.866
MF burden (0–3)	3.0 [3.0, 3.0]	3.0 [2.0, 3.0]	.015
SMT burden (0–3)	3.0 [3.0, 3.0]	3.0 [2.5, 3.0]	.261
ANG burden (0–3)	3.0 [3.0, 3.0]	3.0 [1.5, 3.0]	.117
OC burden (0–3)	2.5 [2.0, 3.0]	1.0 [0.1, 1.0]	.008
MMSE (max = 30)	24.0 [19.0, 27.0]	26.0 [22.8, 27.8]	.272
Number of BNT sessions	3.0 [2.0, 3.0]	3.0 [2.0, 4.0]	.566
Age at BNT (years)	65.0 [59.0, 72.0]	64.0 [57.8, 65.5]	.391
BNT (% correct)	83.3 [80.0, 86.7]	36.7 [11.7, 71.7]	.047
Number of digit sessions	3.0 [3.0, 4.2]	4.0 [3.0, 4.5]	.482
Age at digit span (years)	65.0 [58.5, 72.5]	64.0 [62.0, 68.0]	.829
Forward span (max)	4.0 [3.0, 4.5]	6.0 [5.0, 7.0]	.008
Sex = Male (%)	6 (46%)	9 (56%)	.867
Phenotype (%)			<.001
lvPPA	11 (85%)	2 (12%)	
svPPA	0 (0%)	11 (69%)	
naPPA	2 (15%)	3 (19%)	

Abbreviations: AD, Alzheimer's disease; ANG, angular gyrus; BNT, Boston Naming Test; FTLD, frontotemporal lobar dementia; lvPPA, logopenic variant primary progressive aphasia; MF, middle-inferior frontal gyrus; MMSE, Mini-Mental State Examination; naPPA, non-fluent/agrammatic primary progressive aphasia; OC, occipital cortex; PPA, primary progressive aphasia; SMT, superior-middle temporal gyrus; svPPA, semantic variant primary progressive aphasia. Notes: Descriptive statistics across autopsy-confirmed AD and FTLD patients. Median and interquartile range (median [IQR]) are provided for continuous variables. Age, MMSE, BNT, and Forward Span are at baseline (first test session). MF, SMT, ANG, and OC burden are at autopsy. Mann-Whitney-Wilcoxon performed pairwise comparisons; *P*-values are reported. For sex (female, male) and phenotype (lvPPA, svPPA, naPPA), frequencies and percentages (%) are reported and chi-square tests compare distribution across groups; *P*-values are reported.

**TABLE 2** Mixed effects models for BNT, Forward Span, and MMSE

	BNT		Forward Span		MMSE	
	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>
Disease duration	64.3	<.001	23.6	<.001	86.3	<.001
Pathology	0.0	.832	1.9	.169	0.1	.711
Phenotype	18.9	<.001	4.0	.139	3.1	.209
Age at death	5.0	.025	1.3	.262	6.9	.009
Sex	2.2	.137	1.4	.237	0.0	.934
Education	3.9	.050	0.7	.393	2.6	.107
Duration:Pathology	5.0	.025	5.6	.018	0.0	.969

Abbreviations: BNT, Boston Naming Test; MMSE, Mini-Mental State Examination.

Notes: Analysis of deviance (Type II Wald chi-square tests)  $\chi^2$  and *P*-value are reported for each fixed effect. Individual was included as a random effect for all models.

clinical features that are sensitive to the distinct histopathologies in the PPA spectrum. To support an in vivo pathological diagnosis for PPA patients, this study investigated the pathological specificity and longi-

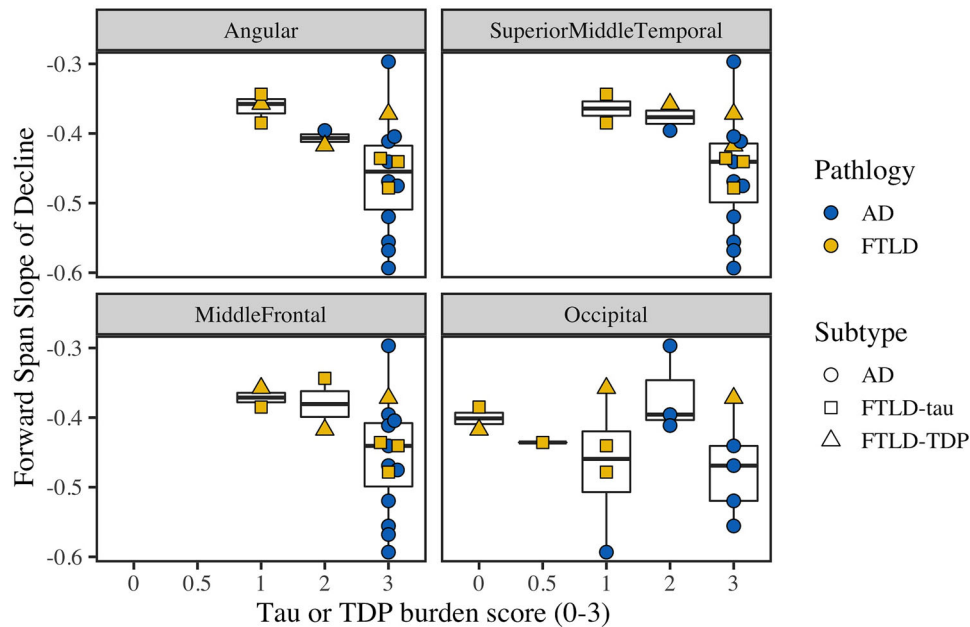
**TABLE 3** Comparison of interaction and null models

A. BNT models	AIC	BIC	logLik	$\chi^2$	Df	<i>P</i>
Null	832	858	-406			
Interaction	829	857	-404	4.9	1	.028
B. Span models	AIC	BIC	logLik	$\chi^2$	Df	<i>P</i>
Null	312	336	-146			
Interaction	308	335	-143	5.4	1	.020

Abbreviations: ANOVA, analysis of variance; BNT, Boston Naming Test.

Notes: Akaike information criterion (AIC), Bayesian information criterion (BIC), and log likelihood (logLik) assess model fit for BNT (A) and Forward Span (B) Models.  $\chi^2$ , degrees of freedom (Df), and *P*-value reported for ANOVAs comparing model fit.

tudinal progression of two core features of lvPPA: naming and repetition. In addition, we assessed the pathologic burden in ROIs implicated in lexical retrieval and the phonological loop: MF, ANG, and SMT.<sup>3,28,48</sup> At baseline, FTLD PPA had lower BNT performance than AD PPA, while AD PPA had shorter repetition spans than FTLD. Longitudinal naming and repetition profiles differed between FTLD and AD, with AD PPA



**FIGURE 3** Forward span decline related to pathologic severity in primary progressive aphasia (PPA) patients with Alzheimer's disease (AD) or frontotemporal lobar dementia (FTLD). Individual rate of decline in forward span by pathological tau or TAR DNA-binding protein (TDP) accumulation. Color indicates pathology (AD, FTLT) of PPA patients. Shape indicates pathological subtype (AD, FTLT-tau, FTLT-TDP)

patients showing significantly steeper decline in both BNT and Forward Span over time, compared to FTLT. The worse decline observed in AD cannot be easily explained by overall worse disease severity: there was no difference in baseline or longitudinal MMSE across AD and FTLT. Both BNT and Forward Span rates of decline were directly related to *post mortem* pathological burden in left peri-Sylvian language ROIs, but not to the reference region OC. Thus, molecular pathology in ANG, SMT, and MF appear to contribute to progressive naming and repetition impairment in PPA.

Patients do not always fit cleanly into syndromic categories: there are not infrequent exceptions to a syndromic diagnosis within the PPA spectrum,<sup>13,46,47</sup> particularly true for lvPPA.<sup>4,5,15,17</sup> We therefore pursue a modified approach<sup>12,19,20,48</sup> that focuses on specific language features and their relationship to underlying pathology. We tested two objective assessments of naming and repetition. First, BNT assessed lexical retrieval. Our results demonstrate that BNT may be sensitive to the progression of lexical retrieval impairment in PPA with AD over the course of disease. By contrast, many PPA with FTLT, particularly those with TDP-43 pathology, demonstrated floor effects for BNT early in disease, consistent with profound naming impairments observed in svPPA. Second, Forward Digit Span was used as a surrogate for repetition. While sentences or phrases are commonly used to measure repetition, forward span is easily scored and avoids other factors that can confound judgments of repetition accuracy, such as speech errors common in naPPA.<sup>4,28</sup> Moreover, because poor repetition due to impaired auditory short-term memory is a core feature of lvPPA, these patients can easily show floor effects when repeating lengthy materials. Our results indicate that forward span may be useful for tracking the progressive decline in repetition in PPA patients with AD.

Our findings of repetition decline in AD PPA are corroborated by past work in living lvPPA patients, albeit lacking gold-standard autopsy data.<sup>28,49,50</sup> While others also report that the rate of naming decline most robustly distinguishes performance in PPA variants compared to other language measures,<sup>51</sup> these investigators found more rapid decline in naPPA and svPPA than in lvPPA. The basis for this discrepancy is unclear. Given the lack of pathological data, it is possible that a subset of naPPA or svPPA patients in that study had undetected underlying AD neuropathology. It is important to emphasize that naming difficulty is embedded in the syndromic characterization of PPA,<sup>2</sup> and that lexical retrieval impairment is ubiquitous in all PPA, albeit to varying degrees.<sup>12,22</sup> Based on our work here, repetition is not only selectively more impaired at baseline but also over the course of disease in PPA with AD, compared to PPA with FTLT. Additional work is needed to determine other factors that might influence clinicopathological correlations in PPA, such as differences in disease severity or the presence of mixed pathologies. Regardless of the basis for discrepant findings, our data indicate that longitudinal performance likely reflects the PPA syndrome and underlying neuropathology more reliably than cross-sectional data.

Rare studies have examined regional pathology in each clinical PPA syndrome,<sup>11,21</sup> although pathology was not directly related to specific language features. Here, we tested how naming and repetition performance related to regions implicated in lexical retrieval and the phonological loop—SMT, ANG, and MF.<sup>3,48</sup> Our results support the hypothesis that accumulating pathology in these regions may contribute to the declining performance we observed in PPA with AD. Neither naming nor repetition were associated with OC pathology burden, indicating that contributions of the peri-Sylvian network to naming and

repetition performance are specific. These results are corroborated by in vivo neuroimaging studies that have associated these brain regions in PPA with naming and repetition difficulty.<sup>24,50,52,53</sup> While ANG and SMT are particularly vulnerable to AD pathology in PPA,<sup>12</sup> peri-Sylvian regions can also exhibit FTLD spectrum pathology,<sup>31</sup> including prominent involvement in dorsolateral and inferior prefrontal regions in PPA with FTLD-tau.<sup>23</sup> Thus, pathologic accumulation in these and other areas may partially explain naming and repetition difficulty in PPA with FTLD spectrum pathology.<sup>19</sup> Limited histopathological sampling in this study, while according to standardized methods,<sup>32</sup> prevented us from observing regions commonly accumulating FTLD pathology in PPA, such as anterior temporal lobe. Additional large-scale autopsy work integrating *ante mortem* data and examining pathologic burden in cortical regions more prevalent in FTLD is needed to determine the pathologic basis for the full profile of impaired naming and repetition across the clinicopathologic spectrum of PPA. Nonetheless, our data support a role for left hemisphere peri-Sylvian pathology accumulation in the longitudinal decline of naming and repetition.

While the current study aimed to identify clinical features associated with AD pathology in PPA, one important shortcoming is that we were unable to statistically test longitudinal naming and repetition differences between FTLD-TDP and FTLD-tau patients. Figure 2 illustrates large variation in naming and repetition performance within FTLD that may be partially explained by pathological distinctions. However, the small number of FTLD-tau in this study (6 FTLD-tau of 16 FTLD) precluded a robust statistical comparison between FTLD pathological subtypes. Nonetheless, our exploratory analyses in FTLD-tau and FTLD-TDP are consistent with our main findings (see supporting information), indicating more progressive naming and repetition decline in AD with PPA despite differences between FTLD-tau and FTLD-TDP. Longitudinal tracking of naming and repetition in PPA may provide important evidence of underlying pathology, but further work is needed in larger cohorts to understand clinicopathologic relationships, including AD, FTLD-TDP, and FTLD-tau.

Second, in contrast to our previous work in a larger autopsy dataset,<sup>12</sup> we did not observe differences in overall burden between AD and FTLD in two hypothesized regions: SMT and ANG. This may be due to a smaller sample size, as selection criteria required longitudinal clinical data. Moreover, the majority of patients were rated with severe disease (burden score = 3) in many ROIs. Ceiling effects may have obscured differences in pathological accumulation among these individuals. Thus, our ordinal ratings may not capture the full granularity of disease severity compared to more sophisticated, digitized histopathological methods.<sup>31</sup> A related limitation of this retrospective study is that regional sampling was according to standardized methods to provide a pathological diagnosis of AD.<sup>32</sup> Thus, cortical sampling was consistent for ANG, SMT, MF, and OC, the regions included in this study. Conversely, other regions that we hypothesize might relate to BNT or forward span performance in FTLD patients were undersampled, such as inferior frontal gyrus, anterior temporal lobe, and supra-marginal gyrus. Additional detailed histopathologically focused studies are needed to examine the relationship between clinical features and regional patterns of PPA pathology more comprehensively.

Finally, while we demonstrated no difference in global cognitive decline between AD and FTLD PPA, we lacked a full battery of baseline and longitudinal cognitive measures. Discrimination between FTLD and AD pathologies in PPA would be significantly improved by identification of clinical markers that are specific to FTLD pathology, in addition to the AD-specific features we show here.

With these limitations in mind, we conclude that PPA patients with underlying AD neuropathology exhibit more rapid longitudinal decline in naming and repetition, related to pathological accumulation in left-hemisphere peri-Sylvian regions. Because biofluid biomarkers alone may not be sufficient to identify patients with atypical presentations of AD,<sup>18</sup> quantitative longitudinal assessments of BNT and Forward Span may be useful to supplement screening of PPA with underlying AD pathology, and to monitor disease progression in therapeutic trials.

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## CONFLICTS OF INTEREST

K.A.Q.C., J.B., L.A.A.G., N.G.K., Y.B., K.R., E.B.L., J.Q.T., and D.J.I. report no conflicts of interest relevant to this study. M.G. receives research funding from NIH and Biogen; non-financial support for research from Life Molecular Imaging and Avid Radiopharmaceuticals; and participates in clinical trials sponsored by Biogen, Eisai, Alector, Preval, UCB, and PassageBio. M.G. is supported by grants from NIH (AG066597, AG054519, AG052943), the Wyncote Foundation, The Peisach Family Foundation, and the Samuel Newhouse Foundation. Dr. Grossman also receives support as a consultant to PassageBio and Biogen, and in-kind research support from Avid and Life Medical Sciences.

## AUTHOR CONTRIBUTIONS

Conception and design of the study: J.B., K.A.Q.C., M.G., D.J.I. Data acquisition: J.B., K.A.Q.C., M.G., D.J.I., L.A.A.G., K.R., E.B.L., J.Q.T. Data analysis: K.A.Q.C., J.B., N.G.K. Manuscript drafting: K.A.Q.C., J.B., M.G., D.J.I., L.A.A.G., K.R., E.B.L., J.Q.T., N.G.K.

## DATA SHARING

Anonymized data will be shared by a reasonable request from any qualified investigator.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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