

Aphasic variant of Alzheimer disease

Clinical, anatomic, and genetic features

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ABSTRACT

Objective: To identify features of primary progressive aphasia (PPA) associated with Alzheimer disease (AD) neuropathology. A related objective was to determine whether logopenic PPA is a clinical marker for AD.

Methods: A total of 139 prospectively enrolled participants with a root diagnosis of PPA constituted the reference set. Those with autopsy or biomarker evidence of AD, and who had been evaluated at mild disease stages (Aphasia Quotient ≥ 85), were included ($n = 19$). All had quantitative language testing and APOE genotyping. Fifteen had MRI morphometry.

Results: Impaired word-finding was the universal presenting complaint in the aphasic AD group. PPA clinical subtype was logopenic ($n = 13$) and agrammatic ($n = 6$). Fluency, repetition, naming, and grammaticality ranged from preserved to severely impaired. All had relative preservation of word comprehension. Eight of the 15 aphasic participants with AD showed no appreciable cortical atrophy at the individual level on MRI. As a group, atrophy was asymmetrically concentrated in the left perisylvian cortex. APOE $\epsilon 4$ frequency was not elevated.

Conclusions: There is a close, but not obligatory, association between logopenic PPA and AD. No language measure, with the possible exception of word comprehension, can confirm or exclude AD in PPA. Biomarkers are therefore essential for diagnosis. Asymmetry of cortical atrophy and normal APOE $\epsilon 4$ prevalence constitute deviations from typical AD. These and additional neuropathologic features suggest that AD has biological subtypes, one of which causes PPA. Better appreciation of this fact should promote the inclusion of individuals with PPA and positive AD biomarkers into relevant clinical trials. *Neurology*® 2016;87:1-7

GLOSSARY

AD = Alzheimer disease; **AQ** = aphasia quotient; **FDR** = false discovery rate; **FTLD** = frontotemporal lobar degeneration; **NAT** = Northwestern Anagram Test; **NAVS-SPPT** = Sentence Production Priming Test of the Northwestern Assessment of Verbs and Sentences; **NFT** = neurofibrillary tangles; **PPA** = primary progressive aphasia; **PPA-G** = primary progressive aphasia agrammatic subtype; **PPA-L** = primary progressive aphasia logopenic subtype; **PPA-S** = primary progressive aphasia semantic subtype; **SOB** = sum of boxes; **WAB-R** = Western Aphasia Battery-Revised; **WPM** = words per minute.

Primary progressive aphasia (PPA) is diagnosed when language impairment arises in relative isolation and progresses to become the primary obstacle to daily functioning. Frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) are its most common neuropathologic correlates. The primary pathology is frequently FTLD-tau in agrammatic subtypes (PPA-G), FTLD-TDP in semantic subtypes (PPA-S), and AD in logopenic subtypes (PPA-L).¹

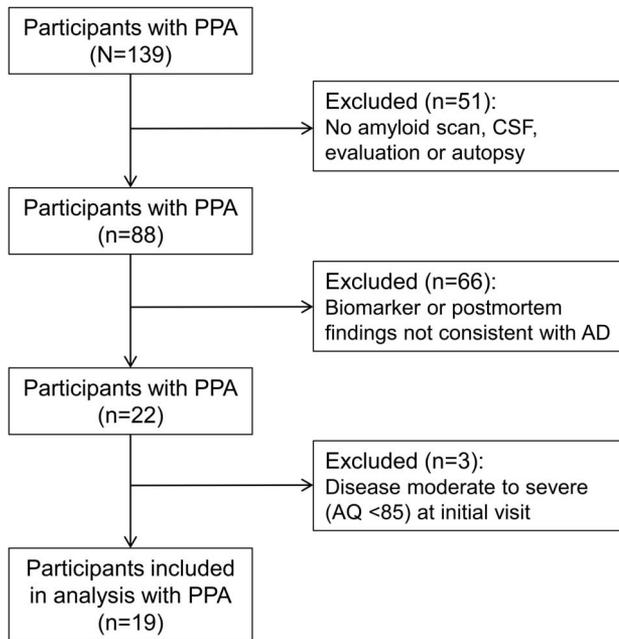
The goal of this report is to characterize the features of PPA associated with AD. Previous investigations were based on samples of convenience with aphasias of variable severity and language testing of limited coverage, especially in the domain of grammar. The current report is based on 19 individuals with a clinical diagnosis of PPA and with postmortem verification or amyloid-PET scans consistent with AD pathology. All participants were enrolled into a prospective project where language measures are quantitatively and uniformly assessed and where cortical morphometry is used to identify regions of peak atrophy. Only participants initially studied at mild stages of aphasia

Supplemental data
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Figure 1 Flowchart showing the selection of participants included in the analysis



AD = Alzheimer disease; AQ = aphasia quotient; PPA = primary progressive aphasia.

were included to emphasize the characteristic features of the early language disturbance and their anatomical correlates as close to disease onset as possible.

Several specific questions were addressed. First, is there justification for equating PPA-L with AD pathology? Second, are there measures of language function characteristic/pathognomonic of PPA associated with AD? Third, is there a consistent pattern of atrophy distribution in PPA associated with AD? Fourth, is the *APOE* genotype frequency in this group different from that seen in more typical amnesic forms of AD?

METHODS The reference set for this investigation consisted of 139 participants with PPA prospectively enrolled into a longitudinal project, with clinical subtype distribution of 32% PPA-G, 18% PPA-L, 23% PPA-S, and 27% unclassifiable by current diagnostic criteria.² Twenty-seven have come to autopsy and an additional 61 have amyloid-PET determinations. Data from these 88 participants were reviewed to identify individuals who had postmortem or biomarker findings consistent with AD and mild aphasia (e.g., initial Western Aphasia Battery–Revised [WAB-R³] aphasia quotient [AQ] ≥ 85). The AQ threshold eliminated individuals where all language functions become compromised and the pattern of the aphasia loses its specificity. Data from the 19 participants who fulfilled these 2 criteria were included in the analyses (figure 1). The PPA diagnosis was based on 3 core criteria: (1) progressive language disorder of recent onset not attributable to elementary motor or perceptual deficits; (2) absence of consequential impairments in episodic memory, visuospatial skills, or comportment for approximately 2 years as ascertained by medical records, structured interviews with family members, and results of

nonlanguage tests (table e-1 at Neurology.org); and (3) diagnostic investigations consistent with a neurodegenerative etiology.^{1,4,5}

Standard protocol approvals, registrations, and patient consents. Northwestern University's Institutional Review Board approved this study. Informed consent was obtained from each participant.

Speech and language assessment. Apraxia of speech was qualitatively rated during clinical assessment (M.-M.M.) by labored output, voice distortions, errors of syllabic stress or duration, mispronunciation of multisyllabic words, and errors of articulatory sequencing that could not be attributed to upper or lower motor neuron dysfunction.⁶ The WAB-R AQ served as a global measure of language impairment.³ Individual language domains were assessed quantitatively with tests previously used to characterize mild PPA.⁵ Fluency (i.e., words per minute [WPM]) was quantified from a recorded story narrative.^{7,8} Sentence production scores on 2 subsets of 15 noncanonical sentences, one from the Northwestern Anagram Test (NAT; flintbox.com/public/project/19927)⁹ and another from the Sentence Production Priming Test of the Northwestern Assessment of Verbs and Sentences (NAVS-SPPT),¹⁰ were averaged to derive a composite score of grammaticality of sentence production.⁵ The NAT does not require oral responses and was specifically designed to dissociate agrammatism from lack of fluency. The ability to understand the syntactic structure of sentences was assessed with the Sentence Comprehension Test of the NAVS, based on a subset of 15 noncanonical sentences of the same type as tested with the NAVS-SPPT and NAT. Repetition was quantitated with the 6 most difficult items from the repetition subtest of the WAB-R (items 10–15, which consist of phrases and sentences).³ Object naming was tested with the Boston Naming Test.¹¹ Single word comprehension was tested with a subset of 36 moderately difficult items (157–192) of the Peabody Picture Vocabulary test.¹² To control for differently scaled variables, quantitative performance scores were transformed into percentages. The WPM counts were transformed into percentages based on the control mean (132 ± 20).⁵ In all other tests, performance of neurologically intact participants of a similar age ($n = 37$) was $\geq 94\%$.⁵

Aphasia classification. The 2011 classification guidelines for PPA-S, PPA-G, and PPA-L were followed with a few modifications.^{2,13} None of the 19 fit the PPA-S criteria. The differentiation of PPA-L from PPA-G is arguably the most challenging aspect of PPA classification.^{13,14} In this study, the diagnosis of PPA-G was made when 2 criteria were met: (1) noncanonical sentence production scores of $\leq 80\%$ on the NAT-NAVS; and (2) presence of agrammatic sentences in recorded narrative or writing samples. The cutoff at 80% performance on the NAT-NAVS test was empirically chosen based on a prior investigation of PPA subtyping at mild impairment stages.⁵ Participants with word-finding deficits and hesitations in speech, whose single word comprehension was intact, who did not fulfill the 2 criteria for agrammatism described above, and whose repetition score was under 90% were classified as PPA-L. This left 2 unclassifiable patients who had all the other features of PPA-L (including logopenic speech with prominent word-finding failures) but whose repetition scores were 91 and 94. We included these patients in the PPA-L group based on our experience that such patients have clinicoanatomic features similar to those with repetition impairments and that they may represent an early stage of PPA-L.^{5,13}

Quantitative MRI morphometry. Structural MRI scans from the initial visit were acquired at Northwestern University's Center for Translational Imaging with a 3.0T Siemens (Munich, Germany) TIM Trio scanner and were reconstructed with the FreeSurfer image

Table 1 Demographics and performance on language tasks

	All PPA, (n = 19)		PPA-L (n = 13)		PPA-G (n = 6)	
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
Age at visit, y	57-79	65 ± 7	57-79	66 ± 8	59-69	64 ± 4
Age at onset, y	50-76	61 ± 7	50-76	62 ± 8	52-66	59 ± 5
Symptom duration at visit, y	1-9	4 ± 2	2-8	4 ± 2	1-9	5 ± 3
Education, y	12-20	17 ± 2	12-20	17 ± 2	13-19	16 ± 3
WAB-AQ	85-97	91 ± 4	87-97	92 ± 3	85-91	88 ± 2
Fluency as percentage of control ^a	35-117	71 ± 22	35-117	72 ± 25	50-82	68 ± 12
Noncanonical sentence production	47-100	80 ± 15	70-100	86 ± 8	47-80	64 ± 16
Noncanonical sentence comprehension	73-100	92 ± 9	73-100	94 ± 8	80-100	87 ± 10
Repetition of phrases and sentences	54-94	78 ± 11	54-94	82 ± 10	61-83	68 ± 8
Object naming	47-98	84 ± 14	47-98	88 ± 13	58-93	77 ± 13
Single word comprehension	81-100	96 ± 5	81-100	96 ± 5	92-100	97 ± 3

Abbreviations: AQ = aphasia quotient; PPA = primary progressive aphasia; PPA-G = primary progressive aphasia agrammatic subtype; PPA-L = primary progressive aphasia logopenic subtype; WAB = Western Aphasia Battery.

^aNumbers beyond 100 indicate hyperfluency in comparison with controls.

analysis suite (version 5.1.0) as previously described.¹⁵ FreeSurfer provides estimates of cortical thickness by measuring the distance between representations of the white-gray and pial-CSF boundaries across each point of the cortical surface.¹⁶ Geometric inaccuracies and topologic defects were corrected using manual and automatic methods based on FreeSurfer's validated guidelines.

Cortical thickness of the PPA group was statistically contrasted against 35 previously described right-handed, age- and education-matched healthy volunteers using spherical surface maps.¹⁷ Differences in cortical thickness between groups were calculated by conducting a general linear model on every vertex along the cortical surface. A stringent false discovery rate (FDR)¹⁸ threshold of 0.001 was used to detect areas of peak cortical thinning (i.e., atrophy) for the PPA group contrast compared to controls.

Neuropathologic and biomarker evidence of AD. The 19 individuals with PPA in this study were selected to have postmortem or in vivo biomarker evidence consistent with Alzheimer pathology. Four of the participants had a primary postmortem diagnosis of AD by National Institute on Aging–Alzheimer's Association criteria.¹⁹ The remaining 15 had amyloid-PET with ¹⁸F-florbetapir, which showed elevated amyloid, defined as the mean cortical standardized uptake value ratio ≥ 1.10 (cerebral-to-cerebellar), using previously described methods for processing.²⁰ This threshold was recommended for detecting neuritic plaques indicative of underlying AD.^{21,22}

RESULTS All participants were right-handed and Caucasian. There were 11 men and 8 women. Symptom onset was under age 65 years in 14 (74%), with 8 reporting onset in the 50s. Daily living activities that did not depend on language were mostly preserved. The mean AQ was 90 ± 4 and the mean Clinical Dementia Rating sum of boxes (SOB) was 0.8 (range 0–3), with 16 PPA participants having SOB scores of ≤ 1 , indicating essentially preserved activities of daily living beyond those that had become difficult due to aphasia.

Individual language measures and subtypes. Impaired word-finding was the presenting complaint and a prominent finding at the initial clinical assessment of all of the PPA participants (table 1). Word-finding hesitation lowered word output fluency in some participants, but not in those who reacted to word-finding failures with lengthy circumlocutions. In fact, 2 individuals had WPM (fluency) scores higher than control values. In the other language measures, performance ranged from severely impaired to nearly intact (table 1). The one exception was single word comprehension, which was universally preserved, with a group mean performance of $96\% \pm 5\%$. Symptoms of apraxia of speech were present in 6/19 individuals (4 PPA-L, 2 PPA-G) but at a level of prominence that was overshadowed by the aphasia.

Thirteen of the participants (68%) were classified as PPA-L. This proportion would drop to 58% if the 2 patients with relatively preserved repetition but logopenic speech were considered unclassifiable. Six (32%) were classified as PPA-G. Table 2 provides examples of agrammatic statements from each of the 6 PPA-G participants and their performance scores on the non-canonical sentence production tasks (NAT-NAVS). Independent *t* tests showed that the PPA-G group was more impaired than the PPA-L group in sentence repetition and their AQ ($p \leq 0.01$, uncorrected) but these differences were not significant with Bonferroni correction. The other measures did not reveal significant group differences (table 1).

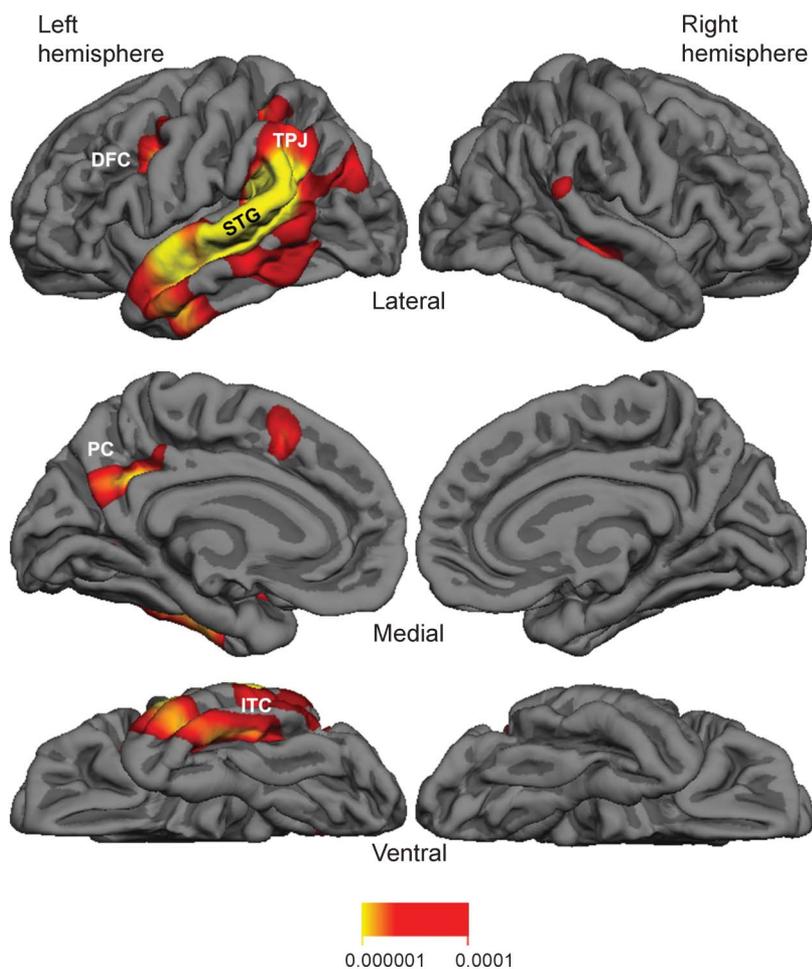
MRI morphometry. Quantitative MRI morphometry was available for 15 participants (11 PPA-L, 4 PPA-G). The group atrophy map of the entire sample ($n = 15$) is shown in figure 2. Peak atrophy sites

Table 2 Examples of agrammatic statements from each of the 6 primary progressive aphasia agrammatic subtype participants and their performance scores on the noncanonical sentence production tasks (Northwestern Anagram Test-Northwestern Assessment of Verbs and Sentences) (% correct)

1. "I going there. A lot of telephoning and receiving telephoning people." (80%)
2. "We stopped to get gas and to go to restrooms. The clerk starting yelley about the key." (47%)
3. "I wanted to go to NY and play with baby...She and I playing with us at play." (57%)
4. "We have up to 3,000 engineers world throughout the globe." (47%)
5. "Joyous yells were shouting to Mr. + Mrs. James to see the success of the kite." (80%)
6. "I placed student is family to go to high school." (77%)

for the group as a whole were concentrated within the lateral temporal cortex, especially the superior temporal gyrus and the adjacent temporoparietal junction of the left hemisphere. Additional patchy atrophy was detected in dorsolateral and medial prefrontal cortex, precuneus, and inferior temporal cortex. Atrophy patterns for the

Figure 2 Group atrophy map (false discovery rate = 0.001) and quantitative morphometry for the 15 individuals with primary progressive aphasia



DFC = dorsal frontal cortex; ITC = inferior temporal cortex; PC = precuneus; STG = superior temporal gyrus; TPJ = temporoparietal junction. Numbers below the heat map represent p values.

clinical PPA-L and PPA-G subgroups yielded no significant differences in a direct group comparison (FDR = 0.05).

Scans were also qualitatively assessed (M.-M.M.) at the individual level. Eight out of 15 individual scans had no appreciable cortical atrophy. Each of the remaining 7 showed distinctly asymmetric atrophy mostly encompassing temporoparietal components of the left hemisphere language network.

APOE. Five cases (1 PPA-G and 4 PPA-L) had the $\epsilon 4$ allele of *APOE*. Only one of these was homozygous. The remaining 14 (73%) had an $\epsilon 3,3$ genotype. At the Northwestern Alzheimer's Disease Brain Bank, 26% of the control population ($n = 190$) has at least one $\epsilon 4$ allele, whereas this frequency increases to 59% in those with an amnesic dementia during life and AD at autopsy ($n = 75$).¹ The 27% frequency of $\epsilon 4$ allele carriers in the 19 PPA participants with biomarker evidence or autopsy-confirmed AD reported in the current investigation is similar to control values. These data are consistent with previous reports^{23,24} suggesting the $\epsilon 4$ allele of *APOE* is not a risk factor for clinical PPA or AD pathology in PPA.

DISCUSSION This report is based on 19 participants with PPA with autopsy or biomarker evidence of Alzheimer pathology, examined in the mild stages of the disease at initial assessment. Results are therefore relevant to clinical decision-making at the time of initial evaluation.

The majority of the participants (68%) had been clinically classified as PPA-L, including 2 cases with logopenic speech but preserved repetition. The remaining participants were classified as PPA-G. These proportions are in line with those of an autopsy series of 58 PPA cases examined at various severity stages, in which 69% of all cases with AD pathology as the primary diagnosis had logopenic aphasia.¹ These results seem at odds with another study, also of PPA participants with autopsy or biomarker evidence of AD, where a complete overlap with PPA-L was reported.²⁵ However, in that study, grammatical ability was not reported and 5/14 participants presented with additional nonverbal memory impairments. Some of the participants in that study may, therefore, have qualified for a PPA-G diagnosis and others may have failed to fulfill the root diagnostic PPA criteria, which require a relative sparing of episodic memory.

The converse question of whether all PPA-L is associated with AD reveals equally complex relationships. In the series of 58 autopsies, for example, only 56% of PPA-L cases were associated with a primary neuropathologic diagnosis of AD.¹ Investigations addressing this question with amyloid-PET scans have also yielded variable results. One study reported that 92% of PPA-L participants had positive amyloid scans.²⁶ Two other studies reported lower rates of 66% and 69%, more in line with the autopsy results.^{27,28}

Table 3 Variants of Alzheimer disease (AD)

1. Autosomal dominant, early-onset AD: Caused by amyloidopathy, not related to age or APOE.
2. Late-onset AD: Age and APOE4 related, amnesic phenotype, neurofibrillary tangles (NFT) emerge and reach highest densities in hippocampo-entorhinal complex according to Braak & Braak staging patterns. ³⁵
3. Primarily aphasic AD: Not age or APOE4 related. NFT can violate Braak & Braak staging patterns by being more frequent in language than memory areas. ²³
4. Primarily visuospatial AD (posterior cortical atrophy): NFT can be more frequent in visual areas (Brodmann area [BA] 17, BA 18, and superior colliculus) than the hippocampo-entorhinal complex. ³⁷ Age and APOE dependency remain to be determined.
5. Primarily behavioral/executive (frontal-type) AD: NFT densities in frontal cortex can be greater than in the hippocampo-entorhinal complex. ³⁸ Age and APOE dependency remain to be determined.

While there is evidence that PPA associated with AD is more likely to present as logopenic aphasia and that logopenic PPA is more likely to be associated with AD, there is no one-to-one correspondence. Neither individual measures of language impairment nor clinical subtyping into logopenic vs agrammatic variants can resolve the differential diagnosis. Fluency, repetition, naming, and grammatical ability in individuals with PPA and AD neuropathology, at least in the early stages, may range from preserved to severely impaired and MRI morphometry may initially show no obvious atrophy. Even the presence of speech apraxia, albeit of lesser salience than the aphasia, does not rule out the presence of AD. At the individual patient level, therefore, the nature of neuropathology in a logopenic patient would be difficult to resolve without biomarker evidence.

In the 7 cases with appreciable cortical atrophy on quantitative MRI, the common denominators were profound asymmetry favoring the left hemisphere and greater atrophy of lateral temporal cortex compared to medial temporal areas or the precuneus. The peak atrophy pattern for the group (figure 2) showed a distribution similar to previous reports of atrophy and hypoperfusion in PPA participants with autopsy or biomarker evidence of AD.^{25,27} The concentration of atrophy in the temporoparietal junction and adjacent superior temporal gyrus mirrors atrophy patterns of PPA-L¹³ and is in keeping with the greater representation of logopenic participants in the group atrophy map shown in figure 2. The asymmetrical atrophy distribution in our PPA cohort differs from typical amnesic forms of AD,²⁹ which tends to be symmetric. However, the small patches of atrophy in dorsal frontal cortex, precuneus, and inferior temporal cortex overlapped with areas considered part of the cortical atrophy signature of amnesic dementia with AD.²⁹ The absence of detectable atrophy in the clinical scans of 7 patients reflects the early disease stages represented in this study. Conceivably, more powerful imaging methods could have revealed abnormalities in these cases as well. Practically, however, these results indicate that a clinically unremarkable MRI in an individual with PPA does not rule out underlying AD.

The inclusion of 2 individuals with logopenic speech and relatively preserved repetition deficits under the

PPA-L variant could be viewed as a limitation since this designation does not strictly follow the 2011 consensus criteria.² The alternative would have been to categorize these 2 individuals as unclassifiable, which would decrease the percentage of PPA-L associated with AD and increase the number of PPA phenotypes associated with AD pathology. All in all, the same conclusion could be made; there is no unique correspondence between a single PPA phenotype and AD neuropathology.

Another potential limitation of this study is the reliance on amyloid-PET with florbetapir as the AD biomarker in 15 of the 19 participants. In individuals who had been imaged within 1 year of death, however, the same ligand was shown to offer better than 95% sensitivity and specificity for the postmortem detection of neuritic plaques characteristic of AD.³⁰ It is also conceivable that some of the PPA participants with positive amyloid scans could have an additional FTLD pathology. In 58 consecutive PPA autopsies, such a double diagnosis was encountered in only 1 patient whose postmortem examination met criteria for both AD and FTLD-TDP.¹ The probability that the biomarker-positive PPA participants in the current study were misclassified pathologically is therefore quite low. Furthermore, the 4 autopsy-verified participants were evenly split between the PPA-L and PPA-G phenotypes and would, by themselves, support the conclusion that there is no exclusive relationship between AD and logopenic PPA.

Typical late-onset amnesic AD is commonly associated with language impairments, mostly in the form of anomia. However, such language impairments tend to arise later than the amnesia and play a much less conspicuous role in disrupting customary activities. The current study addresses the entirely different phenotype of PPA where the aphasia is the first and most salient feature. The Alzheimer pathology associated with this phenotype has prominent features that set it apart from the typical amnesic form of this disease. (1) Onset is most commonly before age 65, perhaps explaining why the female predominance of typical AD is not present. (2) Peak atrophy shows an asymmetric predilection for the language-dominant left hemisphere and displays only partial overlap with the atrophy signature of typical AD.²⁹ (3) As previously reported in

an autopsy series,¹ the *APOE* ε4 allele is not a risk factor for the AD that causes PPA. (4) Learning disabilities, including dyslexia, are risk factors for PPA but not amnesic dementias.^{31,32} (5) Neurofibrillary tangles (NFT) can display atypical asymmetric distributions that violate the Braak and Braak pattern by favoring language cortex over mediotemporal limbic areas.²³ (6) Neuritic amyloid plaques may be asymmetrically distributed, favoring the left hemisphere.²⁰ (7) TDP-43 abnormalities, seen in at least 30% of typical AD cases, are not present in the AD pathology associated with PPA.³³ These features indicate that the AD associated with PPA has temporal, anatomic, neuropathologic, and genetic factors that diverge from those of the far more common late-onset and amnesic forms of AD. As shown in table 3, AD can have several variants, some of which, like PPA, are nonamnesic.^{34–38} Individuals with these atypical nonamnesic manifestations tend to be excluded from AD clinical trials, where outcome measures are chosen to emphasize memory function. The advent of molecular biomarkers now makes it possible to identify a sizable contingent of such individuals with underlying AD pathology. Their inclusion in clinical trials will offer them equal access to novel agents and will require the introduction of new outcome measures designed to assess the relevant nonamnesic domain of the primary cognitive impairment.

AUTHOR CONTRIBUTIONS

M.-M.M. and E.R. contributed to conception and design of the study; A.M., B.R., J.S., K.C., D.C., S.W., C.T.K., E.B., M.-M.M., and E.R. collected and analyzed the data; M.M. and E.R. drafted the manuscript.

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DISCLOSURE

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