RESEARCH ARTICLE OPEN ACCESS

Association of Regional Atrophy With Naming Decline in Primary Progressive Aphasia

Bonnie L. Breining, PhD, Andreia Vasconcellos Faria, MD, Donna Clark Tippett, MA, MPH, Melissa Dawn Stockbridge, PhD, Erin L. Meier, PhD, Brian Caffo, PhD, Olivia Hermann, MA, Rhonda Friedman, PhD, Aaron Meyer, PhD, Kyrana Tsapkini, PhD, and Argye Elizabeth Hillis, MD, MA

Correspondence
Dr. Hillis
argye@jhmi.edu

Neurology® 2023;100:e582-e594. doi:10.1212/WNL.0000000000201491

Abstract

Background and Objectives

Primary progressive aphasia (PPA) is a neurodegenerative condition that predominantly impairs language. Most investigations of how focal atrophy affects language consider 1 time point compared with healthy controls. However, true atrophy quantification requires comparing individual brains over time. In this observational cohort study, we identified areas where focal atrophy was associated with contemporaneous decline in naming in the same individuals.

Methods

Cross-sectional analyses–related Boston Naming Test (BNT) performance and volume in 22 regions of interests (ROIs) at each time point using Least Absolute Shrinkage and Selection Operator (LASSO) regression. Longitudinal analysis evaluated changes in BNT performance and change in volume in the same ROIs.

Results

Participants (N = 62; 50% female; mean age = 66.8 ± 7.4 years) with PPA completed the BNT and MRI twice (mean = 343.9 ± 209.0 days apart). In cross-sectional left inferior frontal gyrus pars opercularis, superior temporal pole, middle temporal gyrus, and inferior temporal gyrus were identified as critical for naming at all time points. Longitudinal analysis revealed that increasing atrophy in the left supramarginal gyrus and middle temporal pole predicted greater naming decline, as did female sex and longer intervals between time points.

Discussion

Although cross-sectional analyses identified classic language areas that were consistently related to poor performance at multiple time points, it was not increasing atrophy in these areas that lead to further decline: longitudinal analysis of each person's atrophy over time instead identified nearby but distinct regions where increased atrophy was related to decreasing performance. The results demonstrate that directly examining atrophy (in each individual) over time furthers understanding of decline in PPA and reveal the importance of left supramarginal gyrus and middle temporal pole in maintaining naming when areas normally critical for language degenerate. The novel results provide insight into how the underlying disease progresses to result in the clinical decline in naming, the deficit most common among all 3 PPA variants.

From the Johns Hopkins University School of Medicine (B.L.B., A.V.F., D.C.T., M.D.S., E.L.M., O.H., K.T., A.E.H.), Baltimore, MD; Johns Hopkins University (B.C.), Bloomberg School of Public Health, Baltimore, MD; and Georgetown University (R.F., A.M.), Washington, DC.

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The Article Processing Charge was funded by the authors.

Glossary

BNT = Boston Naming Test; **LASSO** = Least Absolute Shrinkage and Selection Operator; **NACC** = National Alzheimer Coordinating Center; **PALPA** = Psycholinguistic Assessments of Language Processing in Aphasia; **PPA** = primary progressive aphasia; **ROI** = regions of interest.

Primary progressive aphasia (PPA) is a neurodegenerative condition with heterogeneous neuropathologic causes.[1] It predominantly impairs language, while other cognitive functions remain relatively intact. Three main variants have been distinguished.[2] Logopenic variant PPA impairs short-term phonological memory and is linked to atrophy in left posterior perisylvian or parietal regions. Nonfluent/agrammatic variant PPA leads to agrammatism in language production and/or apraxia of speech and involves left posterior frontoinsular atrophy. Semantic variant PPA impairs naming and single-word comprehension and is associated with anterior temporal atrophy, predominantly in the left hemisphere.

Most of what we know about brain-behavior relationships is PPA comes from cross-sectional investigations. In such studies, researchers typically attribute poor performance to dysfunction of regions that seem grossly atrophied or that are reduced in volume or cortical thickness relative to the brains of healthy individuals.[3-13] Some longitudinal studies have investigated the overall progression of the atrophy in the different variants, finding more diffuse atrophy and widespread language impairment over time.[14-21] However, there are few reports connecting behavioral decline on specific tasks to increasing atrophy in specific areas (although see Ref. 22 from our group). Our primary research question was as follows: Is further behavioral decline linked to (1) continuing atrophy of critical language regions that are first affected or (2) atrophy of additional regions that may have been playing a compensatory role in processing? To investigate this question, comparisons of each individual's brain images over time are required. Here, we used longitudinally collected data to examine both atrophy and language decline over time to more directly connect brain and behavior changes. We chose to look at naming performance as all 3 variants of PPA typically experience naming difficulty and are likely to show additional decline over time in this function. We recognize that progressive naming difficulty reflects distinct underlying deficits across variants and even across individuals. For example, individuals with nonfluent agrammatic PPA might make naming errors because of apraxia of speech, and those with semantic variant might make naming errors because of impaired semantic representations of the objects being named. These errors would likely be reflected in different naming error types. However, we use naming accuracy to illustrate the usefulness of the approach for evaluating changes in brain volume associated with changes in language, rather than to identify neural regions critical for the various cognitive and motor processes underlying naming. We also conducted more traditional cross-sectional analyses separately considering the data collected at the time of the first and second scan, so the methods could be compared. We hypothesized that cross-sectional analyses at multiple time points would yield results that are complementary to directly examining longitudinal changes in volume and performance over the same period.

Methods

Participants

A convenience sample of 62 individuals with PPA (31 female; mean age = 66.8 ± 7.37 years) recruited from 2 studies that included longitudinal imaging: a PPA treatment study (PI: KT) at Johns Hopkins University School of Medicine and a treatment study (PIs: RF and AM) at Georgetown University and Johns Hopkins participated from 2010 to 2021. PPA diagnoses were based on presentation with progressive language impairment without accompanying cognitive, behavior, or personality changes.[2,6] Detailed language and cognitive assessments, history, comprehensive neurologic examination, and available neuroimaging were used to classify participants as having logopenic variant (N = 24), nonfluent/agrammatic variant (N = 26), or semantic variant (N = 11) PPA according to the consensus guidelines.[2] The batteries covered the same domains of language (naming, word and sentence comprehension, repetition, syntactic processing, reading, spelling, and nonverbal semantics), but with different tests. For 1 of the studies, the following language tests were administered: Boston Naming Test (BNT)[23]; Hopkins Assessment of Naming Actions[24]; Letter Fluency (F,A,S); Semantic Fluency (Fruits and Animals); Subject-relative, Object-relative Active, Passive sentence comprehension[25]; Spelling to Dictation (JHU Dysgraphia Battery Probability List)[26]; National Alzheimer Coordinating Center (NACC) Frontotemporal Lobar Degeneration Module[27] Sentence Repetition subtest; Temple Assessment of Language and (Verbal) Short-Term Memory in Aphasia[28] Sentence Repetition and Nonword Repetition, Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)[29] subtest 47: Spoken Word-Picture Matching; and PALPA subtest 48: Written Word-Picture Matching. Conceptual semantics was assessed with the Pyramids and Palm Trees Test short version[30] and Kissing and Dancing Test short version (unpublished version of 3). More general cognitive tests included Mini-mental State Examination,[32] Digit Span Forward, Digit Span Backward, Spatial Span Forward, Spatial Span Backward, NACC Story Immediate and Delayed Recall (Verbatim & Paraphrase),[33] Digit Symbol Substitution, Raven Progressive Matrices,[34] and Wechsler Memory Scale Paired Associates (Immediate and Delayed Recall).[35] For the other study, the following language tests were administered: the BNT, Northwestern Anagram

Table 1 Demographic Information

Participant	Sex	Age	Education	Estimated years since symptom onset	Days between scans	BNT at earlier time point	BNT at later time point	Change in BNT (BNT at earlier time point − BNT at later time point)
Participants with lvPPA								
L1	Female	51	18	0.5	691	50	47	−3
L2	Female	53	16	1.5	120	60	56	−4
L3	Female	54	16	4	246	56	42	−14
L4	Female	55	16	1	262	52	52	0
L5	Female	64	16	2.5	245	34	20	−14
L6	Female	66	12	8	315	40	12	−28
L7	Female	66	18	5.5	917	46	10	−36
L8	Female	67	14	6.5	529	13	2	−11
L9	Female	67	18	2	291	37	28	−9
L10	Female	69	18	1.5	162	22	14	−8
L11	Female	69	18	3.5	736	15	3	−12
L12	Female	70	18	9.5	72	6	10	4
L13	Female	71	16	3.5	317	24	19	−5
L14	Female	71	18	3	318	36	24	−12
L15	Female	71	18	6	181	18	9	−9
L16	Female	73	18	3	611	31	4	−27
L17	Male	51	12	3	260	56	58	2
L18	Male	54	16	1	296	52	30	−22
L19	Male	63	15	4	241	46	46	0
L20	Male	68	18	2.5	622	34	24	−10
L21	Male	69	16	3.5	255	36	30	−6
L22	Male	70	19	4.5	296	7	9	2
L23	Male	72	16	2.5	113	50	48	−2
L24	Male	74	16	7.5	201	54	58	4
Mean		64.9	16.5	3.75	345.7	36.5	27.3	−9.2
SD		7.52	1.87	2.35	219.11	16.45	19.01	10.49
Range		51–74	12–19	0.5–9.5	72–917	6–60	2–58	−36–4
Participants with nfvPPA								
N1	Female	60	16	6	92	30	26	−4
N2	Female	63	18	1.5	220	30	28	−2
N3	Female	66	12	2	288	46	48	2
N4	Female	69	15	5.5	242	10	0	−10
N5	Female	69	18	2	133	42	48	6
N6	Female	70	16	2	210	56	56	0

Continued

Table 1 Demographic Information *(continued)*

Participant	Sex	Age	Education	Estimated years since symptom onset	Days between scans	BNT at earlier time point	BNT at later time point	Change in BNT (BNT at earlier time point − BNT at later time point)
N7	Female	76	16	3	698	44	0	−44
N8	Female	81	12	3	360	37	27	−10
N9	Female		14	3	153	52	44	−8
N10	Male	48	12	1	708	24	0	−24
N11	Male	55	16	4	557	46	35	−11
N12	Male	64	14	1	215	42	54	12
N13	Male	64	16	6	197	46	44	−2
N14	Male	65	16	3	202	56	60	4
N15	Male	65	20	2	248	60	60	0
N16	Male	66	20	10.5	342	48	42	−6
N17	Male	68	15	2.5	663	57	49	−8
N18	Male	69	18	3	226	15	7	−8
N19	Male	70	18	2.5	257	60	58	−2
N20	Male	70	20	2	255	60	60	0
N21	Male	73	17	8	246	52	54	2
N22	Male	74	18	1	667	44	39	−5
N23	Male	75	18	2	764	51	49	−2
N24	Male	78	16	1.5	301	30	24	−6
N25	Male	79	20	1.5	294	46	58	12
N26	Male	80	16	2.5	100	54	56	2
Mean		68.7	16.4	3.15	332.2	43.8	39.5	−4.3
SD		7.71	2.39	2.29	204.38	13.53	19.75	11.00
Range		48–81	12–20	1–10.5	92–764	10–60	0–60	−44–12
Participants with svPPA								
S1	female	59	18	2	193	6	5	−1
S2	female	64	16	2.5	313	16	14	−2
S3	female	65	16	6.5	244	6	4	−2
S4	female	68	16	5.5	715	10	0	−10
S5	female	75	12	5.5	322	2	0	−2
S6	male	59	18	7.5	245	2	6	4
S7	male	61	16	3	737	11	6	−5
S8	male	69	16	2.5	690	5	4	−1
S9	male	71	16	10	253	4	0	−4
S10	male	71	20	3.5	272	14	5	−9
S11	male	75	20	3	171	0	0	0

Continued

Table 1 Demographic Information *(continued)*

Participant	Sex	Age	Education	Estimated years since symptom onset	Days between scans	BNT at earlier time point	BNT at later time point	Change in BNT (BNT at earlier time point − BNT at later time point)
Mean		67.0	16.7	4.68	377.7	6.9	4.0	−2.9
SD		5.85	2.24	2.54	220.62	5.19	4.17	3.99
Range		59–75	12–20	2–10	171–737	0–16	0–14	−10–4
Participant with unclassified PPA								
U1	female	63	16	2	231	24	13	−11
All participants with PPA								
Mean		66.8	16.5	3.64	343.9	34.1	28.0	−6.0
SD		7.37	2.12	2.375	208.98	18.93	21.51	10.05
Range		48–81	12–20	0.5–10.5	72–917	0–60	0–60	−44–12

Abbreviations: BNT = Boston Naming Test; PPA = Primary Progressive Aphasia.

Test,[36] Auditory Word-Picture Matching,[37] Written Word-Picture Matching, Reading and Spelling batteries (unpublished), Pseudoword Repetition (unpublished), Picture Description, Basic Word Discrimination, Embedded Sentences, Word and Sentence Repetition, and Action Naming subtests of the Boston Diagnostic Aphasia Examination.[38] Lexical semantic tests included the word version of the Pyramids and Palm Trees Test,[39] Word version of the Kissing and Dancing Test,[31] Word Sorting from the Cambridge Semantic Battery,[40] and the Synonym Judgment Test.[41] Conceptual semantic processing was assessed with Picture version of the Pyramids and Palm Trees Test, Picture version of the Kissing and Dancing Test, Picture Sorting from the Cambridge Semantic Battery, and the Color Knowledge Test.[37] More general cognitive tests included the Montreal Cognitive Assessment[42] and the Benson Figure Copy and Recall tasks.[43] Demographic information about participants in each variant is presented in Table 1. The variant groups did not significantly differ in age, education, or time since onset. There was a larger proportion of women in the lvPPA group (67% female) as compared with the nfvPPA group (35% female; $z = 2.3$, $p = 0.024$). The only language assessment presented in the table is the BNT because it was the only assessment that was given consistently in both studies from which participants were drawn. Most participants with nonfluent/agrammatic PPA had apraxia of speech, as indicated by at least 1 clinician (speech-language pathologist or neurologist) who evaluated them. However, we do not include these data because there was not a consistent and reliable evaluation for apraxia of speech across studies. One participant was unclassified because the individual did not have any of the core criteria for any variant but had progressive impairment in naming and spelling. Each participant took part in concurrently collected behavioral assessment and MRI at 2 time points (mean = 343.9 ± 209.0 days apart) as part of a treatment study; this interval was not significantly different between variant groups. Data from 2 separate treatment studies were used; comparison of the studies and their treatment effects are not considered here because they are ongoing.

Standard Protocol Approvals, Registrations, and Patient Consents

The studies were conducted with the approval of the Johns Hopkins University Institutional Review Board; all participants provided written informed consent in line with the Declaration of Helsinki.

Behavioral Assessment

The BNT was used to evaluate object naming performance. Participants named black and white line drawings of objects; 25 participants completed the 60-item full-form version,[23] while 39 completed the 30-item short form.[44] Scores were normalized to the same scale by doubling short form scores. Uncued first responses were scored. To illustrate our approach with adequate power, we used the global accuracy score, rather than evaluating areas of atrophy associated with change in particular naming error types.

Neuroimaging Collection and Analysis

High-resolution MPRAGE T1-weighted images were acquired using a 3T MRI scanner with the same imaging parameters at both time points (axial orientation, image matrix of 256 × 256 or 224 × 224 mm, and 120–160 slices, voxel size 1 × 1 × 1 or 1 × 1 × 1.1 mm^3, TR/TE 8.4/3.9 or 8.1/3.7 ms). Two types of analyses were conducted: cross-sectional analyses conducted separately for the earlier and later time points (i.e., at the time of the first and second scan, respectively) and a longitudinal analysis evaluating change between the 2 time points.

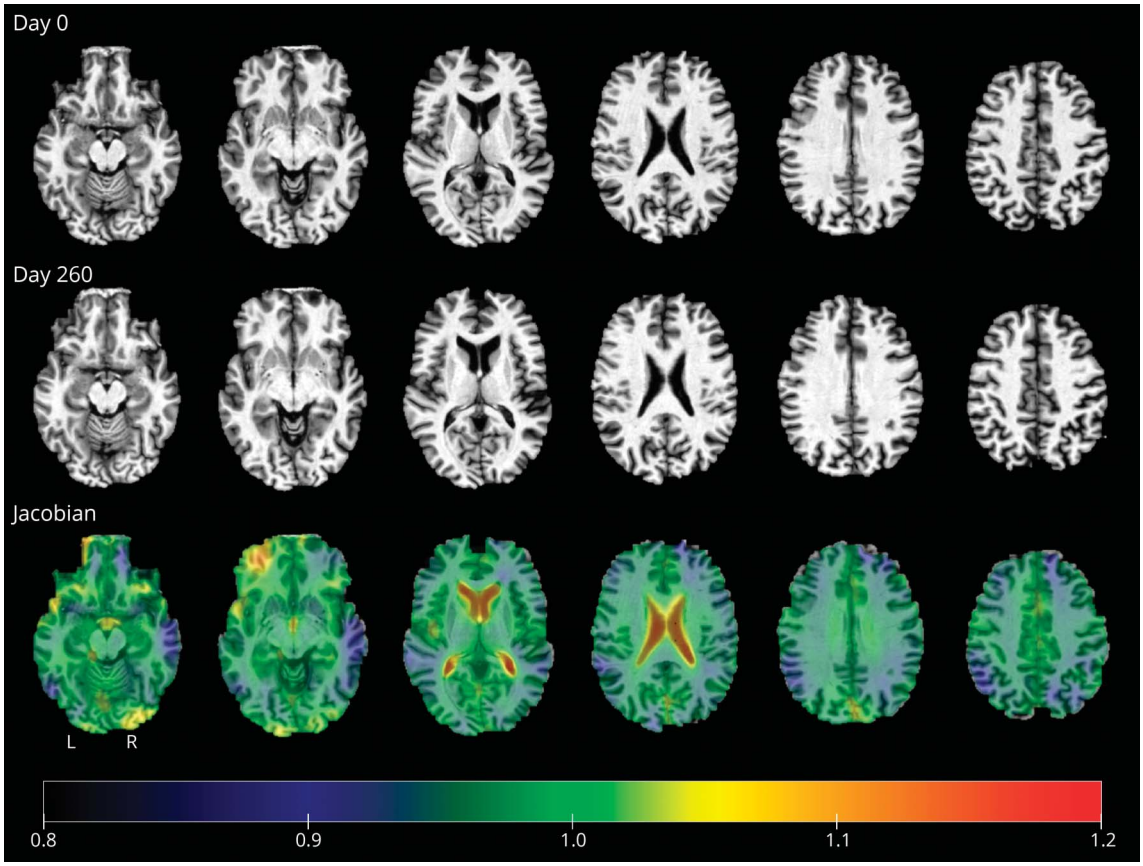
For the cross-sectional analyses, each anatomic scan was segmented into 276 regions through atlas-based analysis in the MRI Cloud platform.[45] In this analysis, each participant's brain is registered to multiple geriatric atlases, labeled based on the atlas parcellation, and then warped back to participant space, using the highly accurate large deformation diffeomorphic metric mapping algorithm and a multiatlas fusion label algorithm. The volume of brain tissue in each region was calculated in MNI space. To control for regional atrophy, we normalized volumes by cerebral volume (total brain volume without myelencephalon and CSF). To control for interindividual brain size differences, we also calculated the ratio of cerebral volume to intracranial volume (total brain volume without myelencephalon) for each scan. We selected 22 of the 276 regions from the automatic parcellation as regions of interests (ROIs): 11 left hemisphere regions that are commonly associated with language and their right hemisphere homologues. These included pars opercularis, pars orbitalis, and pars triangularis of inferior frontal gyrus; supramarginal gyrus; angular gyrus; superior, middle, and inferior temporal gyri; superior and middle temporal poles; and fusiform gyrus. These regions were chosen because they are commonly associated with language and often damaged in PPA.[2-6,8-12]

For the longitudinal analysis, we quantified change in each ROI. For each individual, we used DiffeoMap[46] to align the later scan to the earlier scan, using automated image registration followed by large deformation diffeomorphic metric mapping. The Jacobian determinant, which is the local expansion factor of the large deformation diffeomorphic metric mapping deformation fields, was used to quantify local volume changes at the voxel level. A Jacobian of less than 1 indicates shrinkage relative to the earlier scan, while a Jacobian of greater than 1 indicates expansion. We calculated the mean Jacobian for each of the 22 ROIs used in the cross-sectional analysis, using the parcellation of the earlier scan to define the regions. Figure 1 shows an example Jacobian determinant map. We calculated the mean Jacobian for each of the 22 ROIs used in the cross-sectional analysis, using the parcellation of the earlier scan to define the regions.

Statistical Analysis

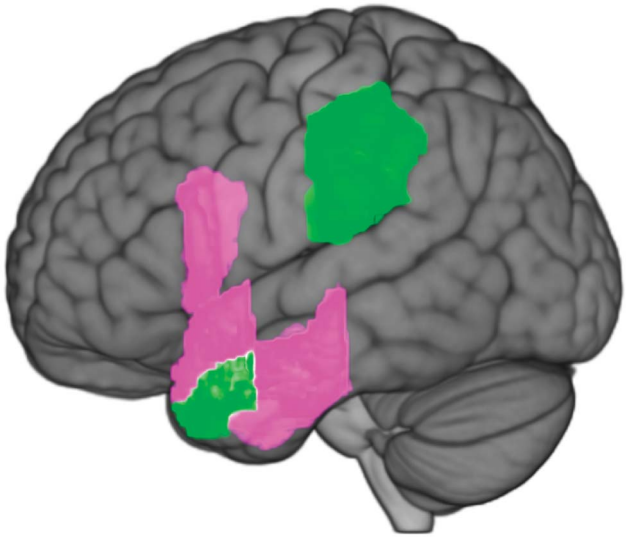
We used Least Absolute Shrinkage and Selection Operator (LASSO) regression[47] to evaluate relationships between naming performance and volume in the 22 ROIs. This method is useful in this situation with a large number of predictors relative to the sample size because LASSO regression performs

Figure 1 Example of a Jacobian Determinant Map



The top of the figure shows the brain of 1 participant with primary progressive aphasia at the earlier time point, labeled day 0. The middle of the figure shows the same individual's brain at the later time point 260 days later. With the naked eye, it is difficult to see exactly where changes are occurring. The bottom of the figure projects a map of the Jacobian determinant for each voxel onto the original brain. A Jacobian determinant of less than 1 indicates shrinkage and is shown in blue/purple, while a Jacobian determinant of greater than 1 indicates expansion and is shown in orange/red. This individual showed expansion of the ventricles and shrinkage in diffuse cortical areas. There is also expansion of sulci in left frontal areas.

Figure 2 ROIs Associated With Naming Performance



Pink regions show areas where smaller volume was associated with worse naming performance on the BNT in the cross-sectional analyses; the same ROIs were identified at both time points. Green regions show areas where greater reduction in volume (i.e., more atrophy) was associated with greater decline in naming performance in the longitudinal analysis. Abbreviations: BNT = Boston Naming Test; ROI = regions of interest.

automated feature selection and shrinkage.[48] The glmnet package in R[49] was used to perform LASSO regression with standardized features, using leave-one-out cross-validation to select the lasso penalty parameter (typically labeled λ) value that resulted in the minimum mean cross-validated error. The selective Inference package[50] was used to conduct inference testing and to calculate *p* values for the selected features.

All analyses used 1-tailed LASSO regression, identifying positive predictors where worse naming performance or greater decline was associated with smaller regional volume or greater increase in atrophy. The cross-sectional models included BNT performance as the dependent variable and volume of each ROI normalized by cerebral volume at the corresponding time point as predictors. The longitudinal model included change in BNT performance (BNT performance at the earlier time point—BNT performance at the later time point) as the dependent variable and the mean Jacobian for each ROI as predictors. All models included cerebral/intracranial volume ratio (at the corresponding time point for the single time point models and the first time point for the longitudinal model) as a measure of overall atrophy, the demographic variable of sex, and estimated years since onset of symptoms. The longitudinal model additionly used initial BNT score at the first time point and the number of days between time points as a predictor. Years since onset and days between time points were reverse coded (as −1*the interval) because we expected longer intervals to predict worse performance and wanted to capture these predictors in the 1-tailed model.

Table 3 LASSO Results—Longitudinal Analysis Predicting Change in BNT Score

	LASSO value	Adjusted coefficient	*p* Value
Model intercept	8.445×10^{-17}		
Left supramarginal gyrus	0.027	0.045	0.782
Left middle temporal pole	0.080	0.143	0.257
Sex (female = −1, male = 1)	0.228	0.335	**0.002**
Days between scans (scan 1 date-scan 2 date)	0.360	0.430	**<0.001**

Abbreviation: BNT = Boston Naming Test.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Table 2 LASSO Results—Cross-sectional Analyses Predicting BNT Score at Each Time Point

	Earlier time point BNT score			Later time point BNT score		
	LASSO value	Adjusted coefficient	*p* Value	LASSO value	Adjusted coefficient	*p* Value
Model intercept	-1.026×10^{-17}			6.155×10^{-17}		
Left inferior frontal gyrus- pars opercularis	0.074	0.149	0.154	0.130	0.193	0.023
Left superior temporal pole	0.377	0.403	<0.001	0.393	0.432	<0.001
Left middle temporal gyrus	0.228	0.276	0.033	0.200	0.256	0.056
Left inferior temporal gyrus	0.203	0.212	0.108	0.101	0.068	0.492
Cerebral to intracranial volume ratio				0.035	0.080	0.493
Estimated years since symptom onset	0.047	0.087	0.431	0.081	0.117	0.159
Sex (female = −1, male = 1)				0.134	0.189	0.016

Abbreviation: BNT = Boston Naming Test.

Table 4 Exploratory Multivariable Models for BNT Score at Each Time Point for the Whole Group and Each Variant, Using Predictors Selected From the Cross-sectional Analyses

	Earlier time point BNT score				Later time point BNT score			
	β	Standard error	*t*	*p* Value	β	Standard error	*t*	*p* Value
All Participants								
Model intercept	−79.265	16.065	−4.93	**<0.001**	−156.850	77.960	−2.01	**0.049**
Left inferior frontal gyrus-pars opercularis	7,386.219	3,851.336	1.92	0.060	11,259.530	5,286.320	2.13	**0.038**
Left superior temporal pole	10,677.005	3,053.668	3.50	**0.001**	12,890.520	3,952.570	3.26	**0.002**
Left middle temporal gyrus	2,853.205	1,283.245	2.22	**0.030**	2,912.310	1709.720	1.70	0.094
Left inferior temporal gyrus	2,569.085	1,603.809	1.60	0.115	884.270	2034.680	0.43	0.666
Cerebral to intracranial volume ratio	NA	NA	NA	NA	82.230	89.630	0.92	0.363
Estimated years since symptom onset	0.693	0.629	1.10	0.275	1.040	0.770	1.35	0.182
Sex (female = −1, male = 1)	NA	NA	NA	NA	4.040	1.830	2.21	**0.032**
lvPPA								
Model intercept	−104.897	41.295	−2.54	**0.021**	−157.395	144.782	−1.09	0.290
Left inferior frontal gyrus-pars opercularis	19,706.948	9,972.115	1.98	0.064	14,885.846	12,976.123	1.15	0.270
Left superior temporal pole	3,570.383	7,386.149	0.48	0.635	9,890.631	9,622.576	1.03	0.320
Left middle temporal gyrus	2,626.653	2,255.530	1.16	0.259	−1945.080	2,970.234	−0.65	0.520
Left inferior temporal gyrus	5,325.838	3,492.436	1.52	0.145	6,868.270	4,421.327	1.55	0.140
Cerebral to intracranial volume ratio	NA	NA	NA	NA	87.218	140.372	0.62	0.540
Estimated years since symptom onset	0.393	1.365	0.29	0.777	0.532	1.597	0.33	0.740
Sex (female = −1, male = 1)	NA	NA	NA	NA	4.841	3.619	1.34	0.200
nfvPPA								
Model intercept	−65.101	29.744	−2.19	**0.041**	−50.020	167.928	−0.30	0.769
Left inferior frontal gyrus-pars opercularis	5,993.884	5,406.523	1.11	0.281	21,865.627	9,102.293	2.40	**0.027**
Left superior temporal pole	12,954.703	4,657.765	2.78	**0.012**	14,360.415	6,812.705	2.11	**0.049**
Left middle temporal gyrus	4,422.998	2027.702	2.18	**0.041**	8,959.556	2,840.985	3.15	**0.006**
Left inferior temporal gyrus	−1852.178	2,822.737	−0.66	0.519	−5,032.391	3,641.926	−1.38	0.184
Cerebral to intracranial volume ratio	NA	NA	NA	NA	−104.008	200.022	−0.52	0.609
Estimated years since symptom onset	0.067	1.067	0.06	0.951	0.764	1.429	0.54	0.599
Sex (female = −1, male = 1)	NA	NA	NA	NA	1.620	3.381	0.48	0.638
svPPA								
Model intercept	1.640	34.649	0.05	0.960	−129.436	14.823	−8.73	**0.003**
Left inferior frontal gyrus-pars opercularis	−2,685.844	4,695.411	−0.57	0.590	−4,923.773	806.888	−6.10	**0.009**
Left superior temporal pole	2,424.863	4,253.205	0.57	0.590	−2,300.817	855.946	−2.69	0.075
Left middle temporal gyrus	353.489	2,955.353	0.12	0.910	−681.858	446.671	−1.53	0.224
Left inferior temporal gyrus	838.632	2,601.266	0.32	0.760	1751.296	370.982	4.72	**0.018**
Cerebral to intracranial volume ratio	NA	NA	NA	NA	174.495	16.731	10.43	**0.002**
Estimated years since symptom onset	0.706	0.824	0.86	0.430	0.304	0.132	2.30	0.105
Sex (female = −1, male = 1)	NA	NA	NA	NA	−0.743	0.298	−2.49	0.088

Abbreviation: BNT = Boston Naming Test.

Table 5 Exploratory Multivariable Models for Change in BNT Score for the Whole Group and Each Variant, Using Predictors Selected From the Longitudinal Analysis

	β	Standard error	*t*	*p* Value
All Participants				
Model intercept	−34.195	32.038	−1.07	0.290
Left supramarginal gyrus	12.239	39.339	0.31	0.757
Left middle temporal pole	23.903	24.333	0.98	0.330
Sex (female = −1, male = 1)	3.342	1.046	3.20	**0.002**
Days between scans (scan 1 date-scan 2 date)	0.021	0.006	3.57	**0.001**
lvPPA				
Model intercept	−31.644	105.925	−0.30	0.768
Left supramarginal gyrus	−8.730	102.183	−0.09	0.933
Left middle temporal pole	40.463	44.891	0.90	0.379
Sex (female = −1, male = 1)	2.485	2.122	1.17	0.256
Days between scans (scan 1 date-scan 2 date)	0.022	0.012	1.89	0.074
nfvPPA				
Model intercept	−75.765	47.356	−1.60	0.125
Left supramarginal gyrus	28.160	58.764	0.48	0.637
Left middle temporal pole	51.387	40.930	1.26	0.223
Sex (female = −1, male = 1)	3.930	1.794	2.19	**0.040**
Days between scans (scan 1 date-scan 2 date)	0.024	0.010	2.35	**0.028**
svPPA				
Model intercept	22.761	31.304	0.73	0.490
Left supramarginal gyrus	−25.376	49.232	−0.52	0.620
Left middle temporal pole	2.148	30.749	0.07	0.950
Sex (female = −1, male = 1)	0.317	1.394	0.23	0.830
Days between scans (scan 1 date-scan 2 date)	0.009	0.007	1.20	0.270

Abbreviation: BNT = Boston Naming Test.

Results

The results are presented in Figure 2. Cross-sectional results relating naming performance and volume in 22 ROIs at each time point using LASSO regression are summarized in Table 2. Longitudinal results evaluating changes in naming performance and changes in volume in the same 22 ROIs are summarized in Table 3. Note that LASSO regression selects a group of features that together predict the outcome; although statistical significance can be estimated for specific features within that group, all selected features are considered important predictors. Although *p* values for the selected features are presented in the tables, they are not discussed in the text. We also created proof-of-concept, exploratory multivariable models with the selected features, both for all participants and for each variant, which are presented in Tables 4 and 5 for cross-sectional and longitudinal analyses, respectively.

In the cross-sectional analysis at the earlier time point, smaller volumes in the left inferior frontal gyrus pars opercularis, left superior temporal pole, left middle temporal gyrus, and left inferior temporal gyrus were associated with worse naming performance on the BNT. As proof of concept, a multivariable model created with all the selected features was significant ($F(5, 56) = 24.4$, $p < 0.001$) and explained 69% of the BNT score at the first time point and 63% after correction for optimism.[27] As an additional exploratory analysis to uncover preliminary information about the relationship between these results and the 3 PPA variants, we also created separate multivariable models with the selected features for each variant. We emphasize the exploratory nature of these models and caution against overinterpretation because there is limited power with the relatively small numbers of participants in each variant group. The model for lvPPA was significant

(F (5, 18) = 4.1, p = 0.012) and explained 53% of the BNT score at the earlier time point, 27% after correction for optimism. In this model, left inferior temporal gyrus volume was a predictor of BNT score that trended toward significance (p = 0.064). The model for nfvPPA was also significant (F (5, 20) = 3.4, p = 0.021) and explained 46% of the BNT score at the earlier time point and 12% after correction for optimism. Left superior temporal pole (p = 0.012) and left middle temporal gyrus (p = 0.041) volumes were significant predictors of BNT score. The model for svPPA was not significant (F (5,5) = 0.6, p = 0.722) nor were any of the individual predictors. It explained 36% of the BNT score at the earlier time point and <0% after correction for optimism.

At the later time point, as at the earlier, smaller volumes in the left inferior frontal gyrus pars opercularis, left superior temporal pole, left middle temporal gyrus, and left inferior temporal gyrus were associated with lower BNT scores. At this time point, female sex and larger cerebral to intracranial volume ratio (i.e., more overall atrophy) also were associated with worse performance. The proof-of-concept multivariable model created with all selected features was significant (F (7, 54) = 13.8, p < 0 .001) and explained 64% of the BNT score at the second time point and 54% after correction for optimism. We created exploratory models for each variant to examine the relationships at the later time point as well. The model for lvPPA was again significant (F (7, 16) = 3.3, p = 0.023) and explained 59% of the BNT score at the later time point and 2% after correction for optimism. However, none of the individual predictors were statistically significant or trended toward significance. The model for nfvPPA was also significant (F (7, 18) = 3.9, p = 0.009) and explained 60% of the BNT score at the later time point and 18% after correction for optimism. There were 3 significant predictors of BNT score: left inferior frontal gyrus pars opercularis (p = 0.027), left superior temporal pole (p = 0.049), and left middle temporal gyrus (p = 0.006) volumes. The model for svPPA was significant (F (7,3) = 39.9, p = 0.006) and explained 99% of the BNT at the later time point and <0% after correction for optimism, suggesting overfitting. Cerebral to intracranial volume ratio (p = 0.002), left inferior frontal gyrus pars opercularis volume (p = 0.009), and left inferior temporal gyrus volume (p = 0.018) were significant predictors of BNT score; sex (p = 0.088) and left superior temporal pole volume (p = 0.075) also trended toward significance.

In the longitudinal analysis relating change in volume to change in performance, increased atrophy (greater negative change) in the left supramarginal gyrus and left middle temporal pole was associated with increased behavioral decline (greater negative change on the BNT). Greater decline in naming was also associated with female sex and larger intervals between time points. The proof-of-concept multivariable model created with all selected features was significant (F (4, 57) = 9.2, p < 0 .001) and explained 39% of the BNT change and 29% after correction for optimism. As in the cross-sectional analysis, we created exploratory multivariable models with the selected predictors for each variant. The model for lvPPA was significant (F (4, 19) = 3.2, p = 0.037) and explained 40% of the BNT change and 4% after correction for optimism. One predictor trended toward significance in predicting the BNT change: the interval between time points (p = 0.074). The model for nfvPPA was significant as well (F (4, 21) = 6.8, p = 0.001) and explained 57% of the variance and 39% after correction for optimism. Sex (p = 0.040) and the interval between time points (p = 0.028) were significant predictors of BNT change. The model for svPPA was not significant (F (4, 6) = 0.6, p = 0.638) nor were any of the individual predictors. It explained 28% of the BNT score at the earlier time point and <0% after correction for optimism.

Discussion

We identified brain regions that are integral to naming performance in participants with PPA using 2 different but complementary methods. First, we performed more traditional cross-sectional analyses, relating volume in ROIs at a given time to naming scores from the same time. Comparing the results of analyses of the same participants at 2 different time points provides 1 opportunity to evaluate change over time. We were also able to look more directly at change over time with a longitudinal analysis that related change in volume in each area to change in performance. Comparing the cross-sectional and longitudinal results demonstrates the utility of each.

In the cross-sectional analyses at both the earlier and the later time points, the same ROIs were identified. Individuals with lower BNT scores had smaller volumes in the left inferior frontal gyrus pars opercularis, left superior temporal pole, left middle temporal gyrus, and left inferior temporal gyrus. These regions are classic language areas that are commonly associated with naming.[2-4,7-13,21]

The results of the earlier and later time point cross-sectional analyses were not identical. At the later time point, greater overall atrophy, as indexed by the ratio of cerebral volume to intracranial volume, predicted worse performance that this factor contributed significantly at the later but not the earlier time point reflects the finding that atrophy becomes more diffuse as PPA progresses.[14-21] Those with more disease progression are in turn likely to demonstrate more impairment on cognitive tasks.

Although the cross-sectional analyses identified areas that were consistently related to naming performance, the longitudinal analysis allowed us to more directly examine where increasing atrophy predicted increasing behavioral decline. Additional atrophy in the critical areas identified in the cross-sectional analysis (left inferior frontal gyrus pars opercularis, left superior temporal pole, left middle temporal gyrus, and left inferior temporal gyrus) was not linked to additional behavioral decline. Instead, we found that naming performance suffered as the left supramarginal gyrus and left middle temporal pole shrank. These areas are part of the language network, and they are anatomically near and connected to the critical naming areas identified at each time point.[2,4,10,12,13,21,22] Because atrophy

spreads to these regions, their original language processing functions and any compensatory naming functions they took on are impaired. The longitudinal analysis also showed that time predicted decline: Greater behavioral decline was observed when there were longer intervals between scans. This is unsurprising given that these participants have a progressive neurodegenerative condition. It is of important that the results reveal that left supramarginal gyrus and middle temporal pole are able to maintain naming accuracy when the neural network that normally supports naming degenerates. Findings show that even in neurodegenerative disease, there can be some reorganization of structure-function relationships to compensate for focal atrophy.

One factor predicted naming decline in both analyses: female sex. In the cross-sectional analyses, female sex predicted worse performance at the later time point but not the earlier time point, suggesting that women showed greater decline on the BNT. To confirm this result, we directly compared the BNT performance of men and women at each time point with Welch 2 sample t tests. Men performed better than women at the later time point (t (58.3) = −2.5, p = 0.015), but not at the earlier time point (t (58.7) = −1.4, p = 0.16). Furthermore, the finding is in line with longitudinal results showing that women experienced greater decline in BNT performance. There was no significant difference in the interval between time points for men and women (t (59.7) = -0.28, p = 0.78), meaning that the increased decline for women is not a result of greater time between scans. The effect was numerically present in all 3 variants, although it did not reach significance in any variant (lvPPA: t (17.1) = −1.9, p = 0.072; nfvPPA: t (10.9) = −1.0, p = 0.338; svPPA: t(9.0) = −0.4, p = 0.725), suggesting that was not driven to any 1 variant. The finding that women with PPA had lower BNT scores than men is consistent with previous findings from our group[49]; however, in contrast to the findings here, our previous work suggested a slower decline in naming for women. The current results are more compatible with aging research suggesting that women older than 50 years experience faster decline in functional status than men.[50] Differences in decline may be influenced by factors beyond the scope of this study, such as health comorbidities, differences in social support, or the general sexual dimorphism in brain development and structure observed in healthy individuals.[51]

Taken together, our results illustrate that directly examining atrophy over time provides a more complete picture of decline in PPA. Our cross-sectional analyses demonstrated that damage in some regions is consistently related to poor naming. However, it is not increasing atrophy in these areas that leads to further decline; our longitudinal analysis instead identified nearby but distinct regions where increased atrophy was related to decreasing performance. The areas of progressive atrophy may be additional language regions in the vicinity of the "core" language areas, and their progressive involvement likely reflects pathologic extension. It is of important that the pathologic extension resulted in further decline in naming, indicating that naming had been supported by these areas for some time. This finding not only advances our understanding of the clinical course of the disorder but also furthers our understanding of the neural instantiation of language.

An important limitation of this study was relatively small sample size because it is unusual for patients with PPA to have multiple scans with the same parameters and contemporaneous language assessment. Because of the small numbers and limited power, we were only able to create exploratory multivariable models for each variant. We were able to identify regions where volumes were individual predictors of naming score for the cross-sectional analysis that differed for the variants in the cross-sectional analysis (e.g., at the earlier time point, left inferior frontal gyrus pars opercularis volume was a trending predictor in the lvPPA group, while left superior temporal pole and left middle temporal gyrus volumes were significant predictors in the nfvPPA group). However, we caution against overinterpretation of these specific results. They provide proof of concept that it is possible to identify different areas driving effects for different variants; however, further analysis is necessary with larger numbers of participants in each variant group to draw specific conclusions. These results were presented as a starting point for further investigation. In the future, it will be interesting to conduct variant-specific analyses considering all ROIs instead of only those selected by analysis of the whole group.

This study has other limitations as well. Because of the particulars of the statistical methods used (e.g., other regions critical for naming that were highly correlated with the selected regions may have been eliminated in the LASSO regression), we cannot make claims about specific regions we did not identify. Notably, some findings could be due to atrophy in regions that are associated with the identified regions. We recognize that the 3 phenotypes of PPA are generally associated with 3 different underlying pathologies that affect different neural networks. However, evidence from several studies shows that peak atrophy in the 3 different phenotypes occurs in 3 rather large ROI,[2,4] which we evaluated. It seems likely, based on the literature, that the distinct neural networks heavily and differentially depend on the associated ROI. We were not able to directly evaluate the distinct networks with the imaging we had available, so we indirectly evaluated them by evaluating atrophy in the associated ROI. Another limitation is that the treatment studies that provided data for this study did not collect biomarker data, such as APOE alleles, CSF biomarkers, or amyloid or tau PET, and few participants have had autopsies to date. Nevertheless, our results are reasonable and demonstrate the promise of the longitudinal methodology we used.

In the future, this type of longitudinal analysis should be applied to understand decline in additional linguistic and cognitive functions in PPA and areas where atrophy is correlated with particular biomarkers. That is, it should be generalizable to other cognitive functions and other neurodegenerative diseases. Future studies may allow us to better characterize decline

in the different variants of PPA and better predict individual prognoses based on specific atrophy patterns. Similar analyses could benefit clinicians and patients studying and management of other neurodegenerative conditions affecting a variety of cognitive functions. With sufficient numbers, comparable analyses could use a voxel-based approach, identifying atrophy in particular voxels associated with particular functions, diseases, or biomarkers, which could provide complementary information to our parcel-based approach.

Acknowledgment

The authors gratefully acknowledge the participants and sources of research funding. We are grateful to Alexandros Afthinos, PhD, for his assistance accessing the MRI scans for analysis.

Study Funding

This work was supported by NIH Grants R01 DC014475 and R01 DC011317. The MRI equipment in this study was funded by NIH Grant 1S10OD021648.

Disclosure

A.V. Faria reports personal fees from anatomy works, outside the submitted work. The other authors have no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* June 14, 2022. Accepted in final form September 14, 2022. Submitted and externally peer reviewed. The handling editor was Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Bonnie L. Breining, PhD	Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andreia Vasconcellos Faria, MD	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in the acquisition of data; analysis or interpretation of data
Donna Clark Tippett, MA, MPH	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in the acquisition of data; analysis or interpretation of data
Melissa Dawn Stockbridge, PhD	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in the acquisition of data; analysis or interpretation of data
Erin L. Meier, PhD	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in the acquisition of data; analysis or interpretation of data
Brian Caffo, PhD	Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD	Analysis or interpretation of data
Olivia Hermann, MA	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in the acquisition of data
Rhonda Friedman, PhD	Georgetown University; Washington, DC	Major role in the acquisition of data
Aaron Meyer, PhD	Georgetown University; Washington, DC	Major role in the acquisition of data
Kyrana Tsapkini, PhD	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in the acquisition of data
Argye Elizabeth Hillis, MD, MA	Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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