Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia

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ABSTRACT

Objectives: To examine the longitudinal course of primary progressive aphasia (PPA) over a 2-year period and to offer quantitative ranges of expected change that could be used to guide the design and evaluation of therapeutic intervention trials.

Methods: Regional changes of cortical thickness and whole-brain cortical volume loss as well as neuropsychological language performance were assessed at baseline and 2 years later in 13 rigorously characterized patients who fulfilled research criteria for logopenic, agrammatic, and semantic PPA subtypes (6 PPA-L, 3 PPA-G, and 4 PPA-S).

Results: There was substantial progression of clinical deficits and cortical atrophy over 2 years. Neuropsychological language performance patterns lost the sharp distinctions that differentiated one PPA variant from another. Nonetheless, the subtype-specific differential impairment of word comprehension vs grammatical processing was largely maintained. Peak atrophy sites spread beyond the initial distinctive locations that characterized each of the 3 subtypes and displayed a more convergent distribution encompassing all 3 major components of the language network: the inferior frontal gyrus, the temporoparietal junction, and lateral temporal cortex. Despite the progression, overall peak atrophy remained lateralized to the left hemisphere.

Conclusions: The results suggest that the unique features, which sharply differentiate the PPA variants at the early to middle stages, may lose their distinctiveness as the degeneration becomes more severe. Given the substantial atrophy over 2 years, PPA clinical trials may require fewer patients and shorter study durations than Alzheimer disease trials to detect significant therapeutic effects. *Neurology*® 2011;76:1804–1810

GLOSSARY

ANOVA = analysis of variance; **AOS** = apraxia of speech; **BNT** = Boston Naming Test; **bvFTD** = behavioral variant frontotemporal dementia; **FDR** = false discovery rate; **ICV** = intracranial volume; **IFG** = inferior frontal gyrus; **NAT** = Northwestern Anagram Test; **PASS** = Progressive Aphasia Severity Scale; **PPA** = primary progressive aphasia; **PPA-G** = agrammatic primary progressive aphasia subtype; **PPA-L** = logopenic primary progressive aphasia subtype; **PPA-S** = semantic primary progressive aphasia subtype; **PPVT** = Peabody Picture Vocabulary Test; **WAB-AQ** = Western Aphasia Battery Aphasia Quotient.

Primary progressive aphasia (PPA) is a clinical dementia syndrome in which language functions decline over time while other cognitive domains remain relatively preserved. There are 3 accepted clinical variants of PPA, which are characterized by the nature of the principal language deficit: agrammatic (PPA-G), semantic (PPA-S), and logopenic (PPA-L).[1] Despite the wealth of investigations characterizing the clinical and anatomic features of PPA and its variants, relatively little quantitative information exists about the longitudinal clinico-anatomic course of cortical atrophy in this syndrome. One study showed that whole brain volume declined by a mean of 1.67% in 1 year for patients with behavioral variant frontotemporal dementia (bvFTD) or PPA.[2] However, this study did not examine the cortical distribution of progressive

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atrophy. This is particularly important in PPA, where the symptomatology closely reflects the cortical location of neuronal loss.

The current prospective study was undertaken to obtain a quantitative assessment of change in the distribution and quantity of neurodegeneration over a 2-year period in 13 patients with PPA. One goal was to provide additional information on the natural course of PPA. Another was to offer anatomically delineated parameters of expected change that could guide the design and evaluation of future therapeutic trials. With respect to nosology, we wanted to determine whether each subtype has a distinctive clinico-anatomic trajectory of progression or whether there was convergence toward a common endpoint of atrophy distribution.

METHODS

Participants. Fifteen patients had a root diagnosis of PPA and longitudinal data. Two patients were excluded from the analysis: one who was severely impaired at the baseline visit (Western Aphasia Battery Aphasia Quotient [WAB-AQ] <65) and another who had a mixed phenotype. Thus, 13 patients with early-to-midstage PPA at their baseline visit (based on WAB and clinical assessment) and 27 cognitively healthy controls of a similar age and education were included in the study (table 1). Age, education, symptom duration, and months between visits were not statistically different between the PPA variants. The core diagnosis of PPA was made on the basis of an isolated and progressive language impairment according to previously published research criteria.[3-5] All patients with PPA completed MRI at their baseline and follow-up visits approximately 2 years later.

Standard protocol approvals, registrations, and patient consents. Participants were recruited from our PPA Research Program, funded by the National Institute on Deafness and Other Communication Disorders, and evaluated at the Cognitive Neurology and Alzheimer's Disease Center at Northwestern University's Feinberg School of Medicine. Written informed consent was obtained from all healthy volunteers and patients (or caregivers of patients) participating in this program. The Northwestern University Institutional Review Board approved the study.

Table 1 Demographic information[a]

	PPA-L	PPA-G	PPA-S	NC
No.	6	3	4	27
Age, y	65.3 (5.9)	60.7 (1.5)	57.8 (3.9)	62.3 (6.6)
% Male	66.6	66.6	25.0	51.9
Education, y	16.5 (1.2)	16.7 (4.2)	16.0 (2.8)	15.8 (2.5)
Symptoms duration	3.4 (2.7)	4.3 (1.2)	4.0 (1.5)	—
Months between visits	23.5 (1.4)	24.0 (1.0)	24.0 (2.2)	—

Abbreviations: NC = normal controls; PPA-G = agrammatic primary progressive aphasia subtype; PPA-L = logopenic primary progressive aphasia subtype; PPA-S = semantic primary progressive aphasia subtype.
[a] Values are mean (SD).

Neuropsychological measures. ***Grammatical processing.*** The 10-item version of the Northwestern Anagram Test (NAT),[6] which measures object-extracted who questions (e.g., Who is the groom carrying?) and subject-extracted who questions (e.g., Who is carrying the bride?), was used as an offline measure of grammatical processing. This instrument was specifically designed to identify patients with the PPA-G variant. In this test, the patient is asked to order single words, each printed on a separate card, to correctly depict the action in a target picture. The NAT was developed to test the ability to order words into a grammatically accurate sentence. It was specifically designed for patients who present with speech production, word comprehension, or word-finding difficulties, or reduced working memory capacity, who may not be able to demonstrate grammatical competence with standard measures of spontaneous production or sentence comprehension.

Semantic processing. A 36-item subset of moderately difficult items (items 157–192) from the fourth edition of the Peabody Picture Vocabulary Test (PPVT)[7] was used as a test of auditory single-word lexical-semantic processing. For this test, the patient is required to match an auditory word representing an object, action, or attribute to one of 4 picture choices. This subset of the PPVT was chosen because of its proven value in subtyping PPA and identifying patients with the PPA-S variant.[8]

Aphasia severity. The WAB-AQ[9] and the Progressive Aphasia Severity Scale (PASS) were used to measure aphasia severity.[10] The Aphasia Quotient represents a summary of test scores from the auditory comprehension, naming, repetition, and spontaneous speech subtests. PASS scores were derived by consensus from 3 raters (E.R., S.W., and C.W.) for the areas of fluency and grammar in speech and for comprehension, using a scale ranging from 0 to 3. Ratings were based on blinded recordings of narrative speech samples and clinical aphasia test scores.

Naming. The Boston Naming Test (BNT) was used as a measure of naming ability. For this test, the patient is asked to name 60 line drawings.

Nonlanguage domains. Neuropsychological assessment of nonlanguage domains is challenging in PPA since most neuropsychological measures are dependent on language. The preservation of memory and behavior at baseline was assessed using a combination of clinical judgment, behavioral scales, and neuropsychological tests that could be performed nonverbally.

Subtyping. We used performance on the PPVT and the NAT as the 2 orthogonal axes for subtyping purposes.[8] In this template, abnormal PPVT and relatively unimpaired NAT represents the clinical signature of PPA-S while the converse characterizes PPA-G. Our criteria are nearly identical to those included in the recently-published recommendations of an international consortium on PPA,[5] with the exception that repetition impairments were not considered core features of the PPA-L subtype in our scheme. The central features of our PPA-L subtype are intermittent word-finding hesitations and phonemic paraphasias. Our subtyping approach has the validation of imaging and postmortem studies where we found a high prevalence of AD pathology in PPA-L,[11] and distinctive atrophy patterns in quantitative MRI.[8] Using these guidelines the present study consisted of 6 PPA-L, 3 PPA-G, and 4 PPA-S patients.

Motor speech impairments. Dysarthria, hypophonia, and cerebellar speech impairments were absent in the patients with PPA-S and patients with PPA-L. Dysarthria was present in one out of 3 patients with PPA-G, while hypophonia and cerebellar

speech problems were absent in all patients with PPA-G. The definition of apraxia of speech (AOS) can be variable. Insofar as labored speech output or phonologic disintegration can be considered manifestations of AOS, the remaining 2 patients with PPA-G had AOS.

MRI acquisition parameters. T1-weighted 3-dimensional magnetization-prepared rapid gradient echo sequences (repetition time = 2,300 msec, echo time = 2.86 msec, flip angle = 9°, field of view = 256 mm), recording 160 slices at a slice thickness of 1.0 mm, were acquired on a 3-T Siemens TRIO system using a 12-channel birdcage head coil. Imaging was performed at the Northwestern University Department of Radiology Center for Advanced MRI.

Image processing. MRIs were processed using the image analysis suite FreeSurfer (version 4.5.0), which is documented and freely available at http://surfer.nmr.mgh.harvard.edu/. Cortical thickness estimates were calculated by measuring the distance between representations of the white-gray and pial-CSF boundaries across each point of the cortical surface. Surface estimations were automated, but required manual checking for accuracy. Surface errors were corrected by manual intervention and incorporated by rerunning the automated FreeSurfer pipeline. The technical details are described in prior publications.[12]

In addition to the whole-brain analysis, which identified the patterns of significant atrophy, the average cortex volume was calculated at each visit to determine global volume loss over 2 years. The cortex volume included the entire cortical ribbon (neocortex).[13] To correct for individual differences in brain size, the average cortical volume for each patient was "normalized" by accounting for their intracranial volume (ICV) using the following formula: normalized cortical volume = (cortical volume/ICV) × 1,000. ICV was derived from the FreeSurfer suite.[14] Normalized cortical volume was calculated for each patient at each visit and volume loss is expressed as the percent change over the 2-year interval [(normalized cortical volume visit 1 − normalized cortical volume visit 2)/normalized cortical volume visit 1) × 100].

Statistical analysis. Preliminary analyses examined the relationships between cortical thickness and age as well as cortical thickness and symptom duration. The correlations were not statistically different from zero; therefore, these variables were not used as covariates in the cortical thickness analysis. Statistical surface maps were generated for each time point using a general linear model that displayed differences in cortical thickness between each of the PPA variants and the cognitively healthy group. The false discovery rate (FDR) was applied at 0.01 to adjust for multiple comparisons.[15]

A repeated-measures analysis of variance (ANOVA) was used to compare total normalized cortical volume between the PPA variants at each visit. Despite small sample sizes, this analysis offers the opportunity to examine longitudinal change by PPA variant. A Pearson correlation was used to examine the relationship between the change in aphasia severity, as measured by the WAB-AQ, and change in total normalized cortical volume in the PPA group.

RESULTS

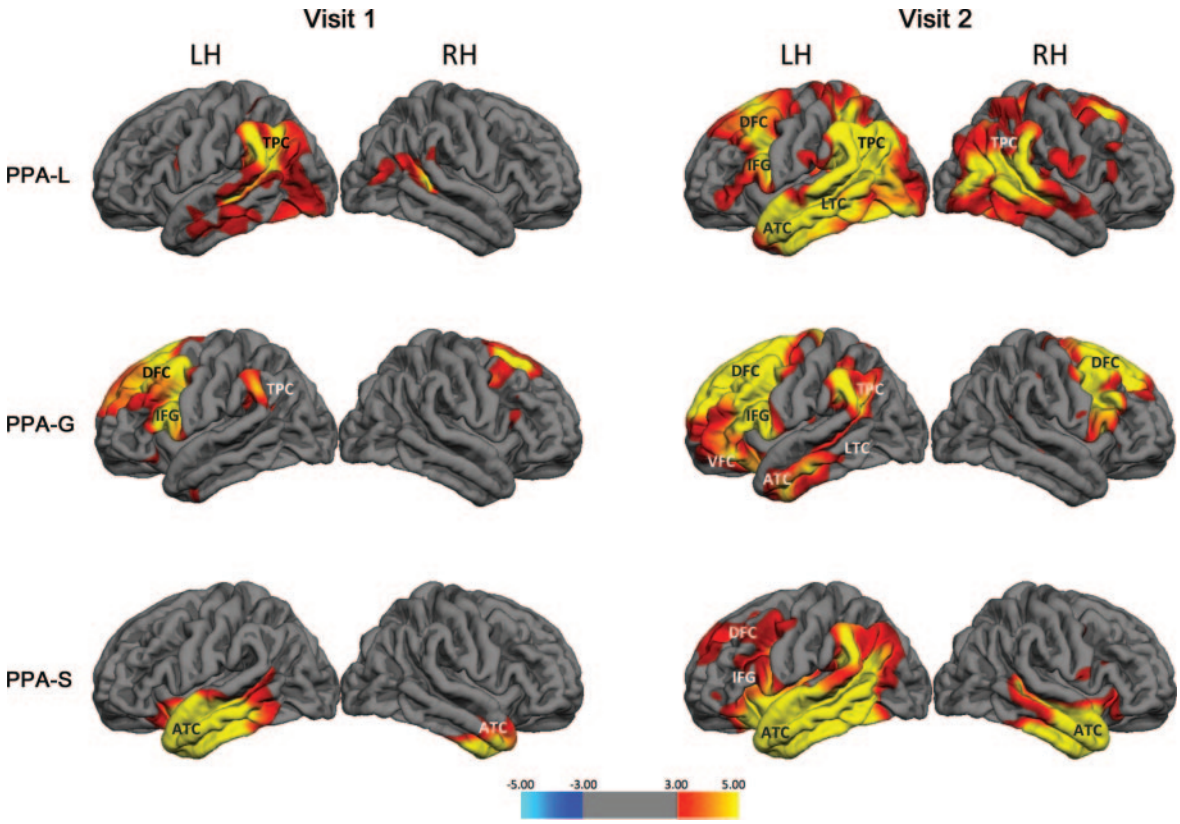
Cortical thickness results by subtype. ***PPA-L.*** At the conservative FDR value 0.01, peak atrophy at the initial visit for the PPA-L group was evident in the temporoparietal region of the left hemisphere and a small region in the right posterior temporal cortex (figure 1). Over the 2-year interval, atrophy spread and encompassed most of the perisylvian cortex, including the inferior frontal gyrus (IFG), with atrophy remaining most severe in the temporoparietal and lateral temporal regions. Significant atrophy was also present in the dorsolateral prefrontal cortex of the left hemisphere and the temporoparietal region of the right hemisphere but the overall asymmetry of atrophy, left hemisphere greater than right hemisphere, was maintained.

PPA-G. Peak atrophy at the initial visit for the PPA-G group included the IFG, dorsal lateral prefrontal cortex, and temporoparietal cortex of the left hemisphere (figure 1). A much smaller area of peak trophy was also present in the dorsal prefrontal cortex of the right hemisphere. The follow-up scan showed that peak atrophy extended from its initial locations to neighboring regions including the dorsal and ventral prefrontal cortex, a greater portion of temporoparietal cortex, and the anterior temporal lobe of the left hemisphere. Peak atrophy sites in the right hemisphere also spread over the 2-year interval to include the IFG, temporoparietal regions, and a larger region of dorsal prefrontal cortex. The leftward asymmetry remained despite the considerable progression of atrophy.

PPA-S. Peak atrophy in the left hemisphere at the initial visit for the PPA-S group was present in the anterior temporal lobe, including the inferior, middle, and superior temporal gyri as well as the pole. Although peak atrophy encompassed the anterior temporal lobe of both hemispheres it was greater in the left than the right hemisphere. After 2 years, peak atrophy was more widespread in the left hemisphere and included the entire left temporal lobe, the temporoparietal cortex, as well as frontal regions, including the IFG (figure 1). The right hemisphere atrophy also extended posteriorly over the 2-year visit interval so that a greater portion of the temporal lobe contained peak atrophy sites. Still, the overall leftward asymmetry of atrophy was maintained.

Cortical volume loss. Total cortical volume loss reflected change in cortical thickness for all parts of the cerebral cortex, and was not confined to regions of peak atrophy shown in figure 1. Results from the repeated-measures ANOVA showed a significant reduction in normalized cortical volume by visit ($F = 124.82$, $p < 0.001$) but there was no main effect of PPA variant ($F = 0.44$, $p = 0.65$) and the PPA variant-by-visit interaction was not significant ($F = 1.61$, $p = 0.25$). The normalized cortical volumes for each subtype by visit were as follows: PPA-L baseline = 266.05 mm^3, follow-up = 247.11 mm^3; PPA-G baseline = 261.45 mm^3, follow-up = 244.07 mm^3; PPA-S baseline = 274.98 mm^3, fol-

Figure 1 Distribution of cortical thinning on the lateral pial surface for each primary progressive aphasia variant compared to a cognitively healthy control group



False discovery rate was set at 0.01 and the flame scale displays significance as a $\log_{(10)} p$ value. ATC = anterior temporal cortex; DFC = dorsal frontal cortex; IFG = inferior frontal gyrus; LH = left hemisphere; LTC = lateral temporal cortex; PPA-G = agrammatic primary progressive aphasia subtype; PPA-L = logopenic primary progressive aphasia subtype; PPA-S = semantic primary progressive aphasia subtype; RH = right hemisphere; TPC = temporoparietal cortex; VFC = ventral frontal cortex.

low-up = 249.83 mm^3. The percent change of normalized cortical volume loss for the 13 patients as a group was 7.7% ± 2.5, though the percent change varied among individual patients (range 3.7%–11.8%). The PPA-S group demonstrated the greatest normalized cortical volume loss (9.2% ± 2.8), followed by the patients with PPA-L (7.1% ± 2.2), and the PPA-G group showed the smallest volume change (6.6% ± 2.5), although the differences were not significant between the groups ($F = 1.23$, $p = 0.33$), likely due to small subject numbers and intersubject variability.

The percent change in total normalized cortical volume was not significantly correlated with the percent change in WAB-AQ ($p > 0.05$) in the PPA group. These results suggest that the measure of cortical volume provides information about disease progression that is not identical to the WAB-AQ measure of general aphasia severity so that each method of assessment contributes additional value for monitoring disease progression.

Neuropsychological performance. Individual neuropsychological data for language and severity are provided in table 2. Neuropsychological performance for each PPA subtype is summarized with group atrophy patterns in figure 2. Given the few patients per group, statistical analyses were not performed among PPA variants. Because of the increased severity, some patients were unable to complete testing for all measures at their 2-year follow-up visit. In the PPA-L group, 4 out of 6 patients showed marked decline on the BNT (21.9% decline on average across the 6 patients), while single word comprehension, as measured by the PPVT (3.3% decline on average), remained relatively intact. The PPA-G group showed decline on all language measures. In fact, each of the patients was too impaired to complete at least one of the language measures. The PPA-S group demonstrated decreased performance on the NAT and the WAB-AQ but also on the PPVT and the BNT where initial scores were very low. In general, the distinctive neuropsychological patterns of the initial visit became blurred at follow-up, with the patients with PPA-S showing impairments on the NAT indicative of abnormal sentence construction and the patients with PPA-G showing impairments on the PPVT in-

Table 2 Neuropsychological information for each patient by visit

Subject	Visit no.	NAT, %	PPVT, %	BNT, %	WAB-AQ, %	PASS: grammar (speech)	PASS: fluency	PASS: comp.	MMSE
P1-L	1	77	97	98	92	0	0.5	0	30
	2	80	94	86	76	0	1	0	22
P2-L	1	100	100	97	97	0	0	0	27
	2	90	100	98	90	0	0.5	0	29
P3-L	1	NA	NA	90	93	0	0.5	0	26
	2	80	97	65	90	0	0.5	0	27
P4-L	1	90	97	90	87	0	0.5	0	23
	2	[a]	89	32	68	1	2	0.5	5
P5-L	1	100	97	88	97	0	0.5	0	28
	2	80	94	50	94	0	0.5	0	19
P6-L	1	70	100	98	93	0	1	0	28
	2	90	97	98	83	0.5	1	0	20
P1-G	1	50	100	98	82	2	3	0	28
	2	50	72	[a]	24	3	3	0.5	18[b]
P2-G	1	40	94	82	80	1	2	0	20
	2	[a]	53	57	58	1	3	1	11[b]
P3-G	1	50	100	88	75.3	3	3	0	30
	2	[a]	[a]	5	31.9	3	3	2	9[b]
P1-S	1	100	39	5	76	0	0	2	24[b]
	2	[a]	R	2	45	0	1	3	8[b]
P2-S	1	NA	44	3	68	0	0	2	17[b]
	2	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
P3-S	1	100	47	23	88	0	0.5	1	27
	2	90	31	5	81	0	0.5	2	22
P4-S	1	100	28	10	83	0	1	2	27
	2	60	22	3	66	0	1	2	17

Abbreviations: BNT = Boston Naming Test; G = agrammatic primary progressive aphasia subtype; L = logopenic primary progressive aphasia subtype; MMSE = Mini-Mental State Examination; NA = test was not part of battery at the time; NAT = Northwestern Anagram Test; PASS = Progressive Aphasia Severity Scale (Scale 0 = normal, 0.5 = questionable/very mild impairment, 1 = mild impairment, 2 = moderate impairment, 3 = severe impairment); PPVT = Peabody Picture Vocabulary Test; R = refused; S = semantic primary progressive aphasia subtype; WAB-AQ = Western Aphasia Battery Aphasia Quotient.

[a] Too impaired.

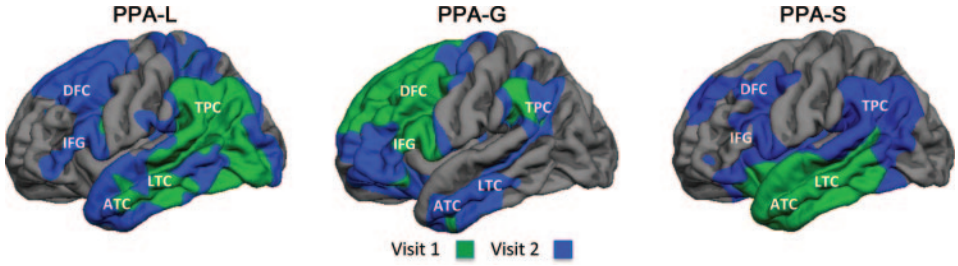
[b] A modified multiple-choice version of the MMSE was given to these patients because of their language difficulties.

dicative of abnormal single word comprehension. However, performance on the NAT remained more impaired than on the PPVT in PPA-G and performance on the PPVT remained more impaired than performance on the NAT in PPA-S. Overall decline in language, as assessed by the WAB-AQ and PASS, was least severe in the PPA-L group. Memory impairments were absent in all patients at the baseline visit. One patient with PPA-G and 3 patients with PPA-S showed behavioral impairments at visit 1.

DISCUSSION The principal finding was the presence of substantial progression of clinical deficits and cortical atrophy over a relatively short interval of 2 years. During this interval, neuropsychological performance patterns lost the sharp distinctions that differentiated one PPA variant from another. Nonetheless, the subtype-specific differential impairment of word comprehension in the PPA-S group vs grammatical processing in the PPA-G group was largely maintained. Peak atrophy sites extended beyond the initial distinctive locations that characterized each of the subtypes and displayed a more convergent distribution, encompassing all 3 major components of the language network: the IFG, the temporoparietal junction, and lateral temporal cortex (figure 2).

Despite the universal progression in all the patients, overall peak atrophy remained distinctly lateralized to the left hemisphere (figure 1). The gradual blurring of

Figure 2 Progression of cortical thinning in the left hemisphere by subtype



Areas of significant cortical thinning in the left hemisphere at baseline (green) and 2 years later (blue) for each of the primary progressive aphasia variants. ATC = anterior temporal cortex; DFC = dorsal frontal cortex; IFG = inferior frontal gyrus; LTC = lateral temporal cortex; PPA-G = agrammatic primary progressive aphasia subtype; PPA-L = logopenic primary progressive aphasia subtype; PPA-S = semantic primary progressive aphasia subtype; TPC = temporoparietal cortex.

subtype-specific distinctions in language impairment patterns and peak atrophy sites despite the maintenance of left-sided asymmetry provide further support for the contention that there is nosologic continuity among PPA subtypes, and that the preferential neurodegeneration of the left hemisphere language network is the common denominator for all 3.

There was good clinico-anatomic concordance in the trajectories of progression. The spread of peak atrophy to the IFG was associated with the emergence of abnormalities in grammatical processing (as measured by the NAT) in PPA-S, whereas the spread of peak atrophy to the lateral and anterior temporal lobes was associated with the emergence of single-word comprehension abnormalities (as tested by the PPVT) and anomia (as tested by the BNT) in PPA-G and, to a lesser extent, in PPA-L (figure 2, table 2).

The mean progression of cortical volume loss for the PPA group as a whole was 7.7% ± 2.5 during the 2-year interval, with a range of 3.7% to 11.8%. Even the lowest values in this range are greater than the whole brain volume loss reported for the MCI-DAT continuum.[16] Our values of cortical volume loss are also slightly greater than the highest end of the range previously reported for whole brain volume loss in bvFTD and in the 3 PPA variants.[2] The higher magnitude of the volume loss that we report may reflect the focus on the cortical mantle, which is the principal site of atrophy, rather than on whole brain volume. Although not significant, the rate of cortical volume loss in the PPA-S group was substantially higher than in the PPA-G and PPA-L groups. The nonsemantic patient group, dominated by 6 patients with PPA-L, demonstrated a slower rate of atrophy and progression, and the neuropsychological language impairment seemed less severe in the PPA-L group. However, the few patients in this study encourage cautious interpretation.

There have been 2 additional studies of longitudinal atrophy, one with patients with FTD and examining the semantic variant of PPA.[17,18] Though the methodology was different, the results from the semantic subtype study, which showed a posterior spread of temporal atrophy and decline in word comprehension, were consistent with our findings. Other studies have examined neuropsychological decline in PPA but have not quantified changes in atrophy.[19-22]

The rate of cortical volume loss and of neuropsychological language decline was faster than expected based on our early longitudinal investigations.[21] While the rapidity of progression is discouraging for patients and families, it facilitates the design of clinical trials since it may take less time and fewer patients to detect a significant modification in the expected course of the disease.

A central feature of all neurodegenerative diseases is the temporal evolution of symptomatology. The results suggest that distinctive features, which sharply delineate the PPA variants at the early to middle stages of the disease, may lose their ability to do so as the degeneration becomes more severe. Future studies will show whether a cutoff should be specified for maximal severity, as assessed by the WAB-AQ or the PASS, beyond which subtyping criteria lose their validity. In our clinical experience it has been challenging to obtain valid neuropsychological data from patients with a baseline visit WAB-AQ <65; therefore, this may serve as a helpful cutoff for designating disease as "severe" and unsuitable for subtyping.

DISCLOSURE

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