

Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia

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ABSTRACT

Objective: To test the validity and reliability of a new measure of clinical impairment in primary progressive aphasia (PPA), the Progressive Aphasia Severity Scale (PASS), and to investigate relationships with MRI-based cortical thickness biomarkers for localizing and quantifying the severity of anatomic abnormalities.

Methods: Patients with PPA were rated using the PASS and underwent performance-based language testing and MRI scans that were processed for cortical thickness measures.

Results: The level of impairment in PASS fluency, syntax/grammar, and word comprehension showed strong specific correlations with performance-based measures of these domains of language, and demonstrated high interrater reliability. Left inferior frontal thinning correlated with impairment in fluency and grammar/syntax, while left temporopolar thinning correlated with impairment in word comprehension. Discriminant function analysis demonstrated that a combination of left inferior frontal, left temporopolar, and left superior temporal sulcal thickness separated the 3 PPA subtypes from each other with 100% accuracy (87% accuracy in a leave-one-out analysis).

Conclusions: The PASS, a novel measure of the severity of clinical impairment within domains of language typically affected in PPA, demonstrates reliable and valid clinical-behavioral properties. Furthermore, the presence of impairment in individual PASS domains demonstrates specific relationships with focal abnormalities in particular brain regions and the severity of impairment is strongly related to the severity of anatomic abnormality within the relevant brain region. These anatomic imaging biomarkers perform well in classifying PPA subtypes. These data provide robust support for the value of this novel clinical measure and the new imaging measure as markers for potential use in clinical research and trials in PPA. *Neurology*® 2010;75:358–366

GLOSSARY

AD = Alzheimer disease; **BDAE** = Boston Diagnostic Aphasia Examination; **CDR** = Clinical Dementia Rating; **CSB** = Cambridge Semantic Battery; **ICC** = intraclass correlation coefficient; **NACC UDS** = National Alzheimer's Coordinating Center Uniform Data Set; **OC** = older control participants; **PASS** = Progressive Aphasia Severity Scale; **PPA** = primary progressive aphasia; **PPA-G** = agrammatic primary progressive aphasia; **PPA-L** = logopenic primary progressive aphasia; **PPA-S** = semantic primary progressive aphasia; **ROI** = region of interest; **WAB** = Western Aphasia Battery.

Planning clinical trials for primary progressive aphasia (PPA)¹ is challenging, in part because of clinicopathologic heterogeneity^{2,3} and in part because of a paucity of clinical assessment instruments specifically tailored to this population.⁴ Although quantitative performance-based linguistic measures are valuable,⁵ research in Alzheimer disease (AD) has demonstrated that performance-based measures provide only one facet of the clinical picture, while clinician judgment–based ratings of symptom severity provide complementary information that is useful in grading illness severity and prognostication.⁶ The Clinical Dementia Rating (CDR) scale⁷ is such an instrument of widely acknowledged utility in AD clinical research and trials.

Supplemental data at
www.neurology.org

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At present, PPA symptom rating instruments are lacking—language ratings are not part of the original CDR, and the new language supplement in the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS)⁸ is a single global rating that captures overall level of language impairment but does not differentiate specific language domains. Since the predominant domain of language impairment relates to the localization of atrophy/hypometabolism and this localization appears to relate probabilistically to molecular neuropathology,⁹ it would likely be of value for both clinical and pathologic investigations to develop additional methods for quantifying impairment in different language domains.

Building on the CDR supplemental language box, we developed and piloted an approach to the rating of symptoms in 3 language domains that have traditionally been employed in PPA clinical characterization—speech fluency, syntax and grammar, and single word comprehension. We also investigated the anatomic correlates of impairment in these domains. These data were then analyzed to determine how well the measures perform in diagnostic sensitivity and specificity. The overall goal of these efforts was to determine whether anatomic measures are a sensitive and specific reflection of the presence and severity of various types of language impairment in PPA, with the aim of using both of these kinds of measures in PPA clinical research and trials.

METHODS **Participants, clinical assessment, and MRI data acquisition.** Forty right-handed participants were studied. Patients with PPA ($n = 23$) were recruited from an ongoing longitudinal study being conducted in the Progressive Aphasia Program in the Massachusetts General Hospital Frontotemporal Dementia Unit, and were evaluated using a structured clinical assessment performed by a behavioral neurologist (B.C.D.) and speech and language pathologist (D.S.). The clinical evaluation of each patient by the neurologist included 1) behavioral observations of the patient's speech and language during a semi-structured interview regarding history of illness, 2) office-based cognitive assessment, 3) neurologic examination, and 4) history from informant. The neurologist's evaluation did not include the use of any formal psycholinguistic instruments (Western Aphasia Battery [WAB], Boston Diagnostic Aphasia Examination [BDAE], Cambridge Semantic Battery [CSB]) and was performed independently. The clinical evaluation of each patient by the speech pathologist included 1) behavioral observa-

tions of the patient's speech and language during a semi-structured interview regarding history of illness; 2) speech-language examination, which included structured conversation (e.g., "What did you do for work?" "How do you spend your weekends?"), picture descriptions, and a brief language assessment similar to that of the Addenbrooke's Cognitive Examination including tasks of naming, repetition, word comprehension, and a motor speech examination; and 3) history from informant. In addition, elements of the WAB, BDAE, and CSB were performed as part of the speech pathologist's evaluation; these quantitative measures were not used in generating Progressive Aphasia Severity Scale (PASS) ratings (see below). The diagnosis of PPA was made if 1) a gradually progressive language disturbance was the most salient symptom prompting the patient/family to seek clinical evaluation; 2) the progressive nature of the deficits and the fact that the language disorder was the chief problem during the initial few years of the disease were documented by the history obtained from the patient and an informant who knows the patient well; and 3) the presence of aphasia was documented by a structured clinical evaluation which also demonstrated the absence of other salient deficits. PPA subtypes (agrammatic [PPA-G], semantic [PPA-S], logopenic [PPA-L], and mixed/other) were diagnosed using an approach similar to that previously described.⁵

In addition, older control participants (OC, $n = 17$; mean age = 70.6 years, SD = 9; 11 female) were included for MRI analyses. As participants in the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort, they undergo a comprehensive annual evaluation by experienced clinicians and were selected for this analysis based on a normal clinical status (CDR = 0).

In this sample, MRI data were acquired using a Siemens Trio 3.0 Tesla scanner (Siemens Medical Systems, Erlangen, Germany). Procedures for data collection included head movement restriction using expandable foam cushions and automated scout and shimming procedures. Two 3-dimensional magnetization-prepared rapid gradient echo sequences were acquired (repetition time/inversion time/echo time 2,300/900/2.98 msec, field of view 256, flip angle 7°, 192 sagittal 1-mm-thick slices, matrix 240 × 256). A fluid-attenuated inversion recovery sequence was visually inspected to rule out nondegenerative pathologies.

Standard protocol approvals, registrations, and patient consents. All participants gave written informed consent in accordance with guidelines established by the Partners Human Research Committee.

Progressive Aphasia Severity Scale. The PASS is a structured clinical instrument, currently under development and modeled after the CDR scale,^{7,10} that aims to provide a semi-quantitative grading of the severity of impairment within a variety of speech and language domains. This 5-point scale enables the clinician to capture change from the patient's pre-morbid baseline. Ratings are made from normal (0) to questionable/very mild (0.5), mild (1.0), moderate (2.0), or severe (3.0) impairment.

The version of the PASS described here is meant to provide an initial elaboration upon the Supplemental Language Box currently in use in the NACC UDS 2.0, which provides a single global rating of language impairment. Based on the hallmark features of progressive aphasia, the first 3 domains of language for which ratings have been developed are fluency of speech, syntax and grammar, and single word comprehension. Scoring criteria are provided in table 1.

Table 1 Abbreviated Progressive Aphasia Severity Scale, version 5.1

	Normal (0)	Questionable/very mild impairment (0.5)	Mild impairment (1)	Moderate impairment (2)	Severe impairment (3)
Fluency: degree to which speech flows easily or is interrupted by hesitations, fillers, pauses; reduced fluency is associated with decreased phrase length and WPM	Normal flow of speech	Speech contains occasional blank pauses or use of fillers (umh); reduced WPM and/or phrase length	Speech is in short phrases, interrupted with pauses or groping for words but there are occasional runs of fluent speech	Dysfluencies in most utterances; phrase length rarely exceeds 3 words	Severely dysfluent speech; phrase length rarely exceeds 1 word; may not speak
Syntax and grammar: use of word forms (run, ran), functor words (the, an), and word order when forming phrases and sentences in speech or writing	No difficulty in the use of grammar and syntax	Occasional agrammatism or paragrammatism (i.e., odd sentence structure such as, "I my car drive in your house"); may complain it is effortful to combine words into phrases or sentences	Frequent agrammatism; sentence structures are simple; frequent misuse/omission of grammatical words or morphology	Utterances contain mostly content words with rare use of syntactic word groupings, functor words, or morphologic markers	Single word utterances or no speech/writing
Single-word comprehension: ability to understand spoken or written single words	No difficulty understanding single words in conversation or testing	Occasional difficulty understanding low-frequency words (e.g., cork); may question the meaning of words (e.g., "What is a ———?")	Displays lack of word comprehension several times in a brief conversation but able to carry on reasonably meaningful conversation	Understands some high-frequency and/or familiar words; questions the meaning of many words in conversation	Minimal comprehension of single words

Abbreviation: WPM = words per minute.

Ratings are made by a clinician after a structured clinical assessment, including interviews separately with the patient and informant and an examination of the patient. These ratings are meant to reflect the clinician's best judgment of the overall level of impairment in each domain based on history of problems in daily life and deficits on examination. As with the CDR, although a number of specific approaches can be used to obtain the information needed to derive this rating, we are working to standardize the questions asked during the interviews and to provide examples of useful examination instruments (material available upon request). Our standard protocol dictates that ratings are first made independently by each clinician (blind to each others' ratings), thus enabling interrater reliability analysis. Once all data are collected and scored, a consensus discussion is employed to adjudicate differences.

We investigated relationships of the PASS ratings to the WAB fluency measure, BDAE grammatic form measure, and CSB word-picture matching measure. Since this analysis was a goal of the present study, PASS ratings were made by the speech pathologist using information from the diagnostic evaluation described above without using the scores on these tests. For the analyses presented here, the neurologist was blind to both the speech pathologist's PASS ratings and the scores on these psycholinguistic measures, using the information obtained from the diagnostic evaluation to determine ratings. Our intent is that, in general use, PASS ratings would be made using the clinician's impression from all data gathered during a diagnostic evaluation. Although all available information should be considered in rating these domains of impairment, the clinician's overall impression of the severity of symptoms in everyday life and of impairment in conversation and examination in the office should be the main contributors to the ratings, with less emphasis on specific language test scores.

MRI morphometric data analysis. The methods employed here have been previously described in detail, including cortical thickness processing and spherical registration to align subjects' cortical surfaces (Freesurfer 4.5.0 [<http://surfer.nmr.mgh.harvard.edu>]).^{11,12}

Based on previous literature,^{13,14} a hypothesis-driven approach using a priori regions of interest (ROIs) was used to investigate whether inferior frontal (pars opercularis) cortical thinning relates to impaired speech fluency with agrammatism while temporopolar thinning relates to impaired word comprehension; ROIs were derived from an automated cortical parcellation¹⁵ and thickness was normalized to the OC sample by calculating a Z score: $Z = (x - \mu_{\text{age-matched OC-s}}) / \sigma_{\text{age-matched OC-s}}$.

Next, we performed an exploratory analysis in which the PASS ratings described above were used as variables in a general linear model correlating each PASS measure to cortical thickness across the entire cortical mantle, as described previously¹⁶ using a threshold of $p < 0.01$, false discovery rate corrected. Finally, we also performed similar exploratory analyses of each of the 3 clinical subtypes of PPA vs the control group.

Statistical analyses. Interrater reliability of the 2 clinicians' independent PASS measures was assessed using intraclass correlation coefficient (ICC). Brain-behavior relationships were investigated using Pearson correlation analysis. Discriminant function analysis (Wilks lambda) was performed to determine how well the anatomic measures would separate PPA subtypes. Statistical analyses were performed using SPSS 16.0 (Chicago, IL) and results were considered significant if $p < 0.01$.

RESULTS Word-finding difficulty was reported as the presenting symptom in about half the participants. Other presenting symptoms included slurring or mispronunciation of words or stuttering or false starts (often phonologic errors on examination), problems using grammar, confusion about word meanings, difficulty understanding idioms, or difficulty reading. Subtype diagnoses included PPA-G, PPA-S, and PPA-L variants. Demographic and clinical characteristics are presented in table 1. Despite deficits in confrontation naming, all patients with PPA-L demonstrated substantial improvements with phonemic cueing or 3-choice recognition, indicating intact semantic knowledge of word meaning.

PASS characteristics. Interrater reliability (between neurologist and speech pathologist) of PASS ratings was high, with ICC >0.9 for fluency (0.99), grammar/syntax (0.99), word comprehension (0.91), and global CDR language (1.0). For subsequent analyses, we use a consensus PASS score of the 2 raters. The degree of impairment reflected by PASS scores was closely related to specific performance deficits, supporting the validity of the scale (table 2). Correlations were present between PASS fluency and WAB fluency ($r = -0.92$) and BDAE grammar ($r = -0.94$), PASS syntax/grammar and WAB fluency ($r = -0.81$) and BDAE grammar ($r = -0.82$), and PASS word comprehension and CSB word-picture matching ($r = -0.87$). The NACC UDS Global Language measure correlated with WAB fluency ($r = -0.59$) and BDAE grammar ($r = -0.66$) but not CSB.

The fluency and grammar/syntax measures for patients in this study were correlated ($r = 0.76$), but word comprehension was not correlated with fluency or grammar/syntax ($p > 0.3$).

Anatomic findings related to symptom severity. Hypothesis-driven analyses demonstrated that left inferior frontal cortical thickness correlated with severity of impairment in fluency ($r = -0.71$) and grammar/syntax domains ($r = -0.57$) but these clinical measures did not correlate with temporal polar thickness (figure 1). Severity of impairment in the comprehension domain correlated with left temporopolar cortical thickness ($r = -0.68$) but not inferior frontal thickness. The CDR global language rating was not correlated with either ROI ($p > 0.1$).

Exploratory maps across the entire cortex focusing on specific symptoms revealed that grammar/syntax was most strongly correlated with thickness in caudal inferior and middle frontal regions, with strong but not complete left lateralization (figure e-1A on the *Neurology*[®] Web site at www.neurology.org).

Since the fluency measure was correlated with the grammar/syntax measure, the exploratory map looks very similar. Comprehension was most strongly correlated with temporopolar thickness (figure e-1B).

Finally, exploratory maps comparing each of the 3 PPA subtypes to controls demonstrated strongly left-lateralized inferior, middle, and superior frontal, precentral, and caudal superior temporal sulcal thinning in PPA-G, strongly left-lateralized superior and middle temporal and inferior parietal thinning in PPA-L, and left-lateralized temporal pole thinning in PPA-S (figure 2).

Diagnostic classification. A stepwise discriminant function analysis aiming to separate PPA subtypes from each other was performed using the a priori ROIs in this study—left inferior frontal gyrus and left temporal pole—as well as 2 ROIs defined in the logopenic subtype in this study—left superior temporal sulcus and left supramarginal gyrus. This stepwise analysis demonstrated that a combination of the left temporal pole, left superior temporal sulcus, and the left inferior frontal gyrus was best at discriminating the 3 PPA subtypes from each other ($\chi^2 = 18.2$, $p < 0.01$), with an accuracy of 100%. Leave-one-out analysis demonstrated an accuracy of 87% (100% PPA-S, 89% PPA-G [1 patient classified as logopenic], and 66% of PPA-L [1 patient classified as semantic and 1 as agrammatic]; figure 3).

DISCUSSION Impairments in patients with PPA are heterogeneous, and quantification is essential for monitoring and the ultimate evaluation of potential treatments. PPA impairments are typically quantified using language test performance measures.^{5,13,17,18} Here we have extended recent work to quantify the overall impairment of language functions through the judgment of trained clinicians, an approach that has traditionally played an important role in AD clinical research and trials. We developed a method for clinician judgment-based grading of overall impairment in fluency, grammar/syntax, and single word comprehension, since these are hallmark language abnormalities in PPA and are often dissociated from each other. The present study demonstrated that this approach is reliable between raters and is valid against performance-based measures. Since performance-based and clinician-rated measures of cognitive impairment are not completely redundant in AD,⁶ it stands to reason that they may provide complementary information in PPA, although this deserves further study. Furthermore, the clinician-graded impairments in fluency/grammar/syntax and comprehension are strongly dissociated with respect to neuroanatomic abnormalities in cortical thickness,

Table 2 Demographic and clinical characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21	Patient 22	Patient 23
PPA subtype	PPA-S	PPA-S	PPA-S	PPA-G	PPA-S	PPA-S	PPA-G	PPA-G	PPA-G	PPA-G	PPA-G	PPA-G	PPA-S	PPA-G	PPA-L	PPA-S	PPA-L	PPA-S	PPA-S	PPA-L	PPA-L	PPA-L	PPA-L
Age, y	59	68	58	70	61	60	66	64	50	79	68	70	68	56	60	59	76	70	53	68	60	70	65
Gender	M	M	M	F	M	F	M	F	F	F	F	M	F	F	F	F	M	F	F	F	M	M	F
Education, y	16	18	12	16	14	15	9	20	16	16	20	12	16	16	12	12	18	12	18	16	18	22	12
Symptom duration, y	3	13	6	8	6	2	6	3	2	3	3	4	4	4	6	4	4	6	5	3	1	5	2
CDR global	1	1	0.5	0.5	0.5	0	0.5	0	0	0.5	0	0.5	0.5	0.5	1	0	0	0.5	0	0.5	0	0	0.5
CDR supplemental-behavior	2	0.5	0.5	0.5	2	0.5	0	0	0	0	0	0	0	0	2	0	0	0.5	0	0.5	0	0	0
CDR supplemental-language	2	2	2	1	1	1	2	0	0.5	2	2	1	2	0.5	2	2	0.5	1	0.5	1	0.5	0.5	1
BDAE Aphasia Severity Rating Scale (0 = severe; 5 = minimal deficit)	1	1	1	3	3	3	1	5	4	2	3	3	2	4	2	3	4	1	3	3	5	4	3
Naming ^a																							
CSB confrontation naming, %	NT	NT	97	19	20	97	NT	97	97	91	100	69	100	86	13	100	78	NT	59	33*	90*	60*	44*
Word knowledge																							
CSB spoken word-picture matching, %	50	22	94	83	53	100	84	100	100	97	100	94	84	100	63	100	N/A	59	98	N/A	N/A	N/A	97
Speech fluency, grammar, and syntax ^b																							
WAB fluency (0 = severe; 10 = normal)	8	6	1	10	10	9	2	9	5	4	0	10	4	9	8	9	9	6	9	8	9	9	6
BDAE grammatical form (1 = severe; 7 = normal) ^c	7	5	1	7	7	7	1	7	5	2	1	7	4	7	7	6	7	7	7	6	7	7	6
Auditory comprehension																							
Following commands, ^d %	NT	7*	NT	75*	93*	88*	30*	100*	93*	100*	100*	38*	61*	80*	20*	100*	95*	43*	100*	90*	100*	100*	84*
PASS-rating																							
Fluency	0.5	1	3	0.5	0	0.5	3	0.5	1	2	3	0.5	2	0.5	0	1	0.5	0.5	0	1	0.5	0.5	2
Syntax/grammar	0	0	3	0	0	0.5	3	0	2	2	1	0.5	2	0	0	0.5	0	0	0	0	0	0	0
Single word comprehension	2	2	0.5	1	1	0	1	0	0	0.5	0	1	0.5	0	1	0	0	2	0.5	0	0	0	0

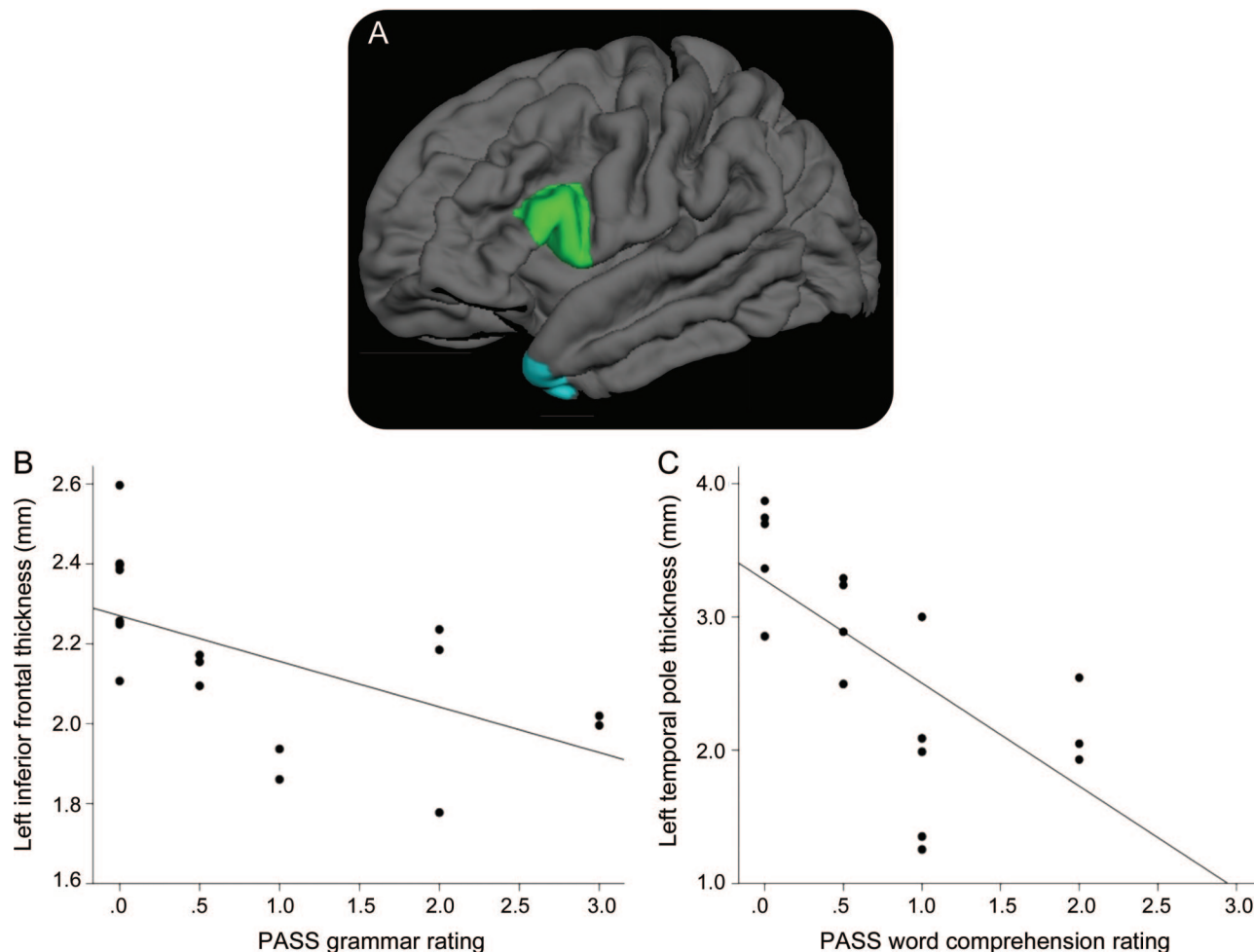
Abbreviations: BDAE = Boston Diagnostic Aphasia Examination-3; CDR = Clinical Dementia Rating; CSB = Cambridge Semantic Battery; N/A = not available; NT = not tested; PASS = Progressive Aphasia Severity Scale; PPA = primary progressive aphasia; PPA-G = agrammatic primary progressive aphasia; PPA-L = logopenic primary progressive aphasia; PPA-S = semantic primary progressive aphasia; WAB = Western Aphasia Battery-revised.

^a Naming: CSB except where indicated by * to indicate Boston Naming Test.

^b Scores were determined by applying the scale to available speech and language samples, which did not always include those from the BDAE and WAB tasks.

^c BDAE grammatical form scale rating descriptions: 1 = no syntactic word groupings; 4 = simplified or incomplete forms; omissions of required grammatical morphemes; 7 = normal range of syntax; normal facility with grammatical words.

^d Following commands: *BDAE Commands task; *WAB Sequential task.



(A) A priori anatomically defined caudal left inferior frontal gyrus (LIFG) ROI and left temporopolar (LTP) ROI were used in this analysis. (B) Correlation between LIFG ROI thickness and grammatic/syntactic impairment ($r = -0.71, p < 0.005$). (C) Correlation between LTP ROI thickness and word comprehension impairment ($r = -0.68, p < 0.003$). PASS = Progressive Aphasia Severity Scale.

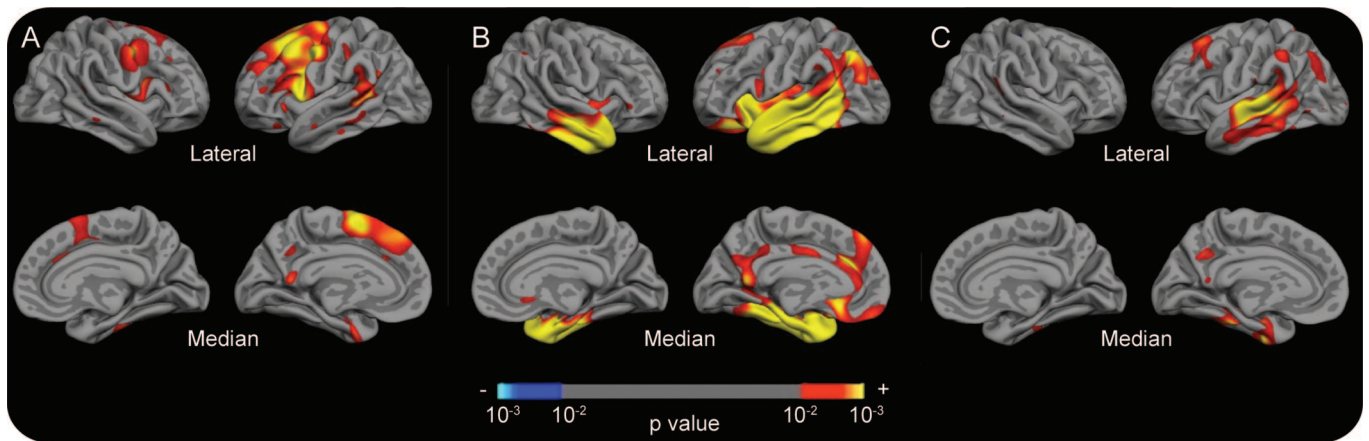
also supporting their validity. Both hypothesis-driven and exploratory analyses demonstrated sensitive and specific relationships between impaired syntax/grammar and ventrolateral prefrontal atrophy, and between impaired word comprehension and temporopolar atrophy.

We have previously shown through longitudinal clinical research in prodromal AD that measures grading both symptom severity in daily life and in the office and performance abilities on psychometric testing can provide complementary information with respect to present level of impairment as well as prognosis.⁶ Every clinician has worked with a patient who exhibits prominent symptoms in daily life yet who performs relatively well on office-based tests. Conversely, there are many patients who have relatively subtle symptoms, maintaining generally good function in complex activities of daily life, yet who perform strikingly poorly on tests. This can be particularly true in some patients with fluent, word

comprehension-centered forms of PPA. Thus, we believe it is critical for the field to continue to develop and apply a rich set of instruments for clinical assessment,⁴ ideally tailored to the PPA population and including patient- and informant-rated questionnaires, performance-based instruments, and clinician-graded measures. A comprehensive battery of such measures will likely be of great value for clinical research and ultimately treatment trials. We hope that the PASS instrument described here is of use for that goal, and that the specific anatomic relationships found here provide data to support its validity.

Previous studies of PPA have demonstrated the relationships between semantic deficits and left temporopolar atrophy^{19,20} as well as deficits in syntactic processing and inferior frontal atrophy.²¹ Yet there have been few investigations of these dissociable relationships within a single sample of patients with PPA.^{5,13,22} The investigation of dissociated deficits in

Figure 2 Regionally specific cortical thinning in primary progressive aphasia (PPA) subtypes

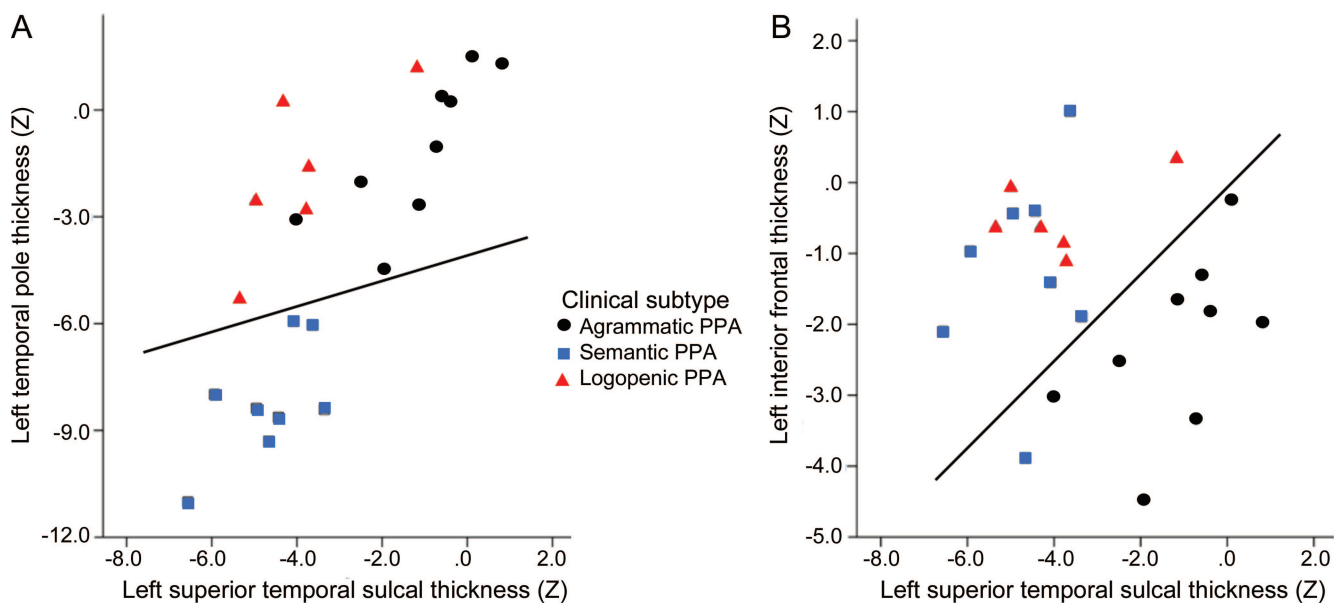


Exploratory analyses of the localization of cortical thinning in (A) PPA-agrammatic patients compared to controls, (B) PPA-semantic patients compared to controls, and (C) PPA-logopenic patients compared to controls. The color scale at the bottom represents the p value of the effects ($p < 0.01$).

single samples of patients with PPA has revealed valuable findings regarding some aspects of language dysfunction in PPA, particularly naming deficits with temporopolar atrophy and nonfluent/agrammatic speech with middle and inferior frontal atrophy.¹³ A recent study employed cortical thickness analysis in comparison with performance-based measures of grammar and semantic processing and found that the patterns of localization of cortical thinning for the 3 subtypes were remarkably similar to those identified here.⁵ Notably, the caudal middle temporal gyrus/superior temporal sulcus—a critical region

for linking speech sounds to word meaning²³—is involved in all 3 variants. Another recent study employing cortical thickness analysis showed a similar pattern of thinning for the PPA-semantic subtype but a somewhat different pattern for PPA-nonfluent subtype, raising questions about whether that sample was truly clinically comparable to the present one.²⁴ One advantage of cortical thickness analysis in this type of work is that the measures can be obtained from single individuals using an a priori ROI approach,¹² and cortical thickness measures are directly related to morphometric measures that can be made

Figure 3 Anatomic measures can accurately discriminate primary progressive aphasia (PPA) subtypes



Discriminant plot of each PPA participant in this study as a function of (A) left temporopolar thickness (y axis) and left superior temporal thickness (x axis) and (B) left inferior frontal thickness (y axis) and left superior temporal thickness (x axis). The use of these 3 anatomic measures can accurately separate PPA-semantic variant patients (squares) from PPA-agrammatic variant patients (circles) from PPA-logopenic variant patients (triangles). Lines are drawn to approximate the discriminability matrix but actual discriminant functions are more complex.

in postmortem brain specimens.^{11,12} Although the cellular and pathologic correlates of cortical thickness have received little study,²⁵ some histologic data indicate that cortical thinning is present in regions that harbor AD pathology.^{26,27} Yet while regional cortical thinning identified via in vivo MRI measures in patients with presumed neurodegenerative syndromes is undoubtedly valuable in localizing pathologic change, it seems much less likely that these regional measures will provide specific evidence regarding the molecular nature of that pathology.²⁸

The congruence between the anatomic classification of patients with PPA using inferior frontal, temporopolar, and superior temporal sulcal thickness and clinical subtyping is impressively good (figure 3), as has similarly been demonstrated using atrophy pattern classification analyses.²⁹ Such findings suggest that these types of quantitative MRI-based measures deserve a place in new clinical diagnostic criteria since they can be applied at the individual level, similarly to recently reported performance-based measures.⁵

Limitations of the present study include the lack of additional domains in the PASS rating scale. It is clear that patients with PPA can exhibit a variety of other relevant symptoms beyond impaired fluency, grammar/syntax, and comprehension. Fluency can be impaired for a variety of reasons (such as impairments in grammar/syntax, phonology, or word retrieval), so this measure may ultimately need to be refined or replaced, but it is useful at present. We have developed ratings for other domains of language function, including word retrieval, repetition, articulation, and others, and are currently testing these measures (the current scale is available upon request). It is also not clear how readily the PASS approach used here will generalize within the community of PPA investigators, but studies are being planned to evaluate its performance at multiple centers. It is not clear how well the PASS will perform in differentiating types of impairment in patients with more advanced stages of illness; it seems to perform very well in mildly to moderately impaired patients. Finally, we do not yet know how well the clinical or anatomic measures employed here will perform in longitudinal analyses, but these investigations are underway. Ultimately, we hope that further investigation will demonstrate that the types of measures studied here can be translated into clinical and imaging markers for use in diagnosis, monitoring, and prognostication, and will prove useful in clinical trials of novel therapeutics for these devastating diseases.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. B.C. Dickerson.

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DISCLOSURE

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