Performance in Specific Language Tasks Correlates With Regional Volume Changes in Progressive Aphasia

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Background: Patterns of language impairment have long been used clinically to localize brain damage in stroke patients. The same approach might be useful in the differential diagnosis of progressive aphasia owing to neurodegenerative disease.

Objective: To investigate whether scores on 4 widely used language tasks correlate with regional gray matter loss in 51 patients with progressive language impairment owing to neurodegenerative disease.

Method: Scores in the Boston Naming Test and in the "repetition" "sequential commands" and the "language fluency," subtests of the Western Aphasia Battery were correlated with voxel-wise gray matter volumes using voxel-based morphometry.

Results: Significant positive correlations were found between each language task and regional brain volumes: (1) naming and the bilateral temporal lobes; (2) sentence repetition and the left posterior portion of the superior temporal gyrus; (3) sentence comprehension and the left dorsal middle and inferior frontal gyri; and (4) fluency of language production and the left ventral middle and inferior frontal gyri.

Discussion: Performance on specific language tasks corresponds to regional anatomic damage in aphasia owing to neurodegenerative disorders. These language tests might be useful in the differential diagnosis of primary progressive aphasia variants that have been previously associated with damage to corresponding anatomic regions.

Key Words: confrontation naming, repetition, sentence comprehension, language fluency, language, neuroimaging, voxel-based morphometry, aphasia, primary progressive aphasia

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Speech and language deficits are common in various neurodegenerative disorders such as Alzheimer disease (AD),[1,2] corticobasal degeneration,[3,4] frontotemporal dementia,[5,6] and progressive supranuclear palsy.[7,8] When the clinical presentation is characterized by relatively isolated language symptoms for the first 2 years, the term primary progressive aphasia (PPA) is applied.[9] Once considered a unitary syndrome associated with widespread perisylvian atrophy, PPA has now been fractionated into several clinical variants, associated with different patterns of cognitive, neuroimaging, and pathologic changes.[10–12] Progressive nonfluent aphasia (PNFA) is associated with left inferior frontal and insular atrophy and is most often caused by non-Alzheimer tau positive frontotemporal lobar degeneration-spectrum pathology.[11,12] Semantic dementia (SD) is instead associated with anterior temporal atrophy and is also most often caused by non-Alzheimer's pathology but of frontotemporal lobar degeneration-Ubiquitin positive type.[10,13] The more controversial logopenic/phonologic variant has been associated with damage to the left temporo-parietal junction[11] and preliminary evidence suggests that atypical distribution of AD pathology might be a frequent cause of this presentation of PPA.[14] In this context, the identification of language tasks that tap into functions supported by specific brain regions involved in each PPA variant is relevant for early differential diagnosis.

Beginning with the first historical cases of Broca,[15,16] patterns of language impairment associated with focal brain lesions have been used to predict the location of anatomic damage in clinical neurology. For instance, it is widely accepted that nonfluent language production with relatively preserved comprehension is associated with lesions in the left posterior frontal cortex, whereas severe language comprehension deficits are caused by left posterior temporal damage.[17] Clinical tests such as the Western Aphasia Battery (WAB)[18,19] and the Boston Diagnostic Aphasia Evaluation (BDAE)[20] were designed as clinical tools to assess different language domains and thus provide aphasia classification. However, these tests were designed for stroke patients, who have anatomically well defined and often isolated brain

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lesions in regions that correspond to specific vascular territories of the interested vessels. In the case of progressive aphasia due to neurodegenerative diseases, regional gray matter loss is less anatomically defined, most often associated with some degree of diffuse atrophy and obviously not influenced by vascular territory. For instance, within the temporal lobe, posterior areas are most commonly damaged in vascular accidents and cause the clinical picture of Wernicke aphasia. In SD, the left antero-inferior temporal region is instead most severely damaged but atrophy often extends to other posterior, medial and ventral temporal areas, to medial frontal regions and to the contralateral temporal lobe.[11,21] The different pattern of brain damage in progressive aphasia might prevent a clear correlation between classic aphasia symptoms and regional anatomic involvement or might show associations not expected from the vascular aphasia literature. To date, studies of neurodegenerative patients have described different patterns of anatomic impairment in groups of patients with specific PPA variants.[11,12,22–24] However, to our knowledge, no study has investigated whether performance on single language tests correlates with regional gray matter volume loss in a large group of patients with progressive aphasia, regardless of clinical variant.

In this study, we used voxel-based morphometry (VBM) to correlate scores on 4 different, widely used language tests (confrontation naming, repetition, sentence comprehension, and language fluency in spontaneous speech production) with voxel-wise gray matter volumes in 51 patients with neurodegenerative disease presenting with predominant speech and language symptoms, 41 of whom met criteria for PPA. We hypothesized that performance in each task would correlate with different sites of anatomic damage within the network of brain regions involved in language processing: (i) confrontation naming with temporal lobes[25]; (ii) repetition with left temporo-parietal regions[26,27]; (iii) sentence comprehension with left inferior and middle frontal and superior temporal gyri[28,29]; (iiii) language fluency with left inferior and middle frontal gyri and anterior insula.[30–32]

MATERIALS AND METHODS

Subjects

Fifty-one native English-speaking, right-handed patients participated in the study. The male-to-female ratio was 27/24 and the mean age was 64.1 ± 8.9 years (Table 1). All patients were evaluated at the Memory and Aging Center, University of California San Francisco by a team of experienced clinicians, including a behavioral neurologist, a neuropsychologist, a speech pathologist, a nurse, and a psychiatrist. The team of clinicians reached a consensus diagnosis for each patient, according to the currently published criteria.[33–36] The consensus diagnosis was based on clinical findings and neuropsychologic pattern of impairment, but specific cut-off scores for each cognitive measure were not used to select patients.

Specific inclusion criteria were the presence of prominent speech or language symptoms at each patient's first evaluation and the availability of a magnetic resonance imaging (MRI) scan within 6 months from the clinical evaluation. Forty-one of the 51 patients met clinical criteria for PPA: 14 with PNFA, 15 with SD, and 12 with logopenic progressive aphasia (LPA). Thirty-one of these patients were described in detail in a previous paper.[11]

We have adopted the classification of PPA in the 3 main variants as previously described in details by our group.[11] Briefly, PNFA is characterized by nonfluent verbal output, apraxia of speech, and agrammatism in both production and comprehension.[23] Patients with SD present with anomia and loss of conceptual knowledge.[37] Patients with LPA, a more controversial variant, present with word finding pauses, repetition problems, and grammar comprehension deficits.[11] The remaining 10 patients did not meet PPA criteria because language impairment was not the only domain affected at presentation (eg, visuospatial, behavioral, motor, and or memory deficits were observed). They were diagnosed with frontotemporal dementia (n = 4), AD (n = 4), or corticobasal degeneration/progressive supranuclear palsy (n = 2). We included this group to create a wide distribution of neuropsychologic scores and gray matter loss within our sample, therefore increasing the power of the correlation analyses. Patients were classified in PPA variants only for the analysis of cognitive data but all patients were entered in the neuroimaging analysis as a single group. The patient population presented with heterogeneous speech and language symptoms, including word finding difficulties, apraxia of speech, impairments in comprehension of words and/or sentences reading and writing problems (Table 1).

All participants underwent a comprehensive neuropsychologic and language evaluation, as previously described.[11,38] The neuropsychologic screening battery comprised standard tests to evaluate language, memory, visuospatial, executive functions, and behavior. Results of neuropsychologic screening and demographic data are reported in Table 1. Specifically, LPA patients had longer disease duration, although not significantly different from the other groups.

Each participant signed informed consent documents and the study was approved by the UCSF Committee for Human Research.

Cognitive and Functional Analysis

As part of a comprehensive speech and language evaluation previously described,[11,38] 4 well-known language tasks were used: Boston Naming Test (BNT) for confrontation naming, WAB Repetition Subtest for repetition, WAB Sequential Commands for sentence comprehension, and WAB Spontaneous Speech Language fluency subtest for language fluency. These are standard language tests used in the clinical settings and they can be failed for different reasons (eg, confrontation naming could be affected by lexical retrieval or semantic

TABLE 1. Demographic and Cognitive Data for the Four Diagnostic Groups

	PNFA Mean (SD)	SD Mean	LPA Mean	Other Mean	All Mean
Age	66.5 (9.0)	63.7 (7.0)	65.1 (9.9)	59.8 (9.6)	63.9 (8.9)
M/F ratio	6/9	9/5	6/4	6/7	27/25
Education	16.0 (2.6)	16.8 (2.4)	17.9 (3.0)	17.6 (1.6)	17.0 (2.5)
Disease duration (y)	4.6 (1.4)	4.7 (2.4)	8.0 (5.3)	5.1 (3.9)	5.2 (3.0)
General cognition					
MMSE (30)	25.5 (4.1)	23.4 (4.2)	22.5 (5.4)	24.8 (6.1)	24.2 (4.9)
Praxis (14)	11.0 (4.0)	11.4 (2.5)	12.9 (1.5)	12.8 (1.2)	11.9 (2.7)
Calculation (5)	3.4 (1.8)	4.2 (1.0)	3.2 (1.0)	4.1 (0.8)	3.7 (1.3)
Digit span backward	2.4 (1.3)*†	4.4 (1.0)	3.3 (1.2)	4.7 (2.0)	3.7 (1.6)
Modified Rey-O delay (17)	8.7 (4.5)	8.8 (3.7)	5.9 (4.4)	6.7 (5.0)	7.7 (4.4)
CVLT-MS 4-trails correct total (36)	20.4 (9.0)	11.9 (5.7)	11.9 (6.6)	18.5 (9.4)	16.1 (8.6)
CVLT-MS 10′ free recall (9)	5.2 (3.7)	1.2 (2.0)‡	1.4 (1.6)‡	3.1 (3.0)	2.9 (3.2)
CVLT-MS recognition (9)	7.9 (1.5)	4.3 (3.1)†‡§	7.6 (2.6)	7.8 (1.2)	6.9 (2.6)
Phonemic fluency	5.4 (3.7)	6.4 (4.5)	9.6 (5.8)	8.7 (3.6)	7.4 (4.6)
Semantic fluency	11.5 (5.5)	4.5 (3.3)†‡	7.3 (4.1)	10.8 (5.0)	8.3 (5.3)
Modified Rey-O copy (17)	12.3 (5.4)	16.2 (1.0)	13.6 (2.7)	13.0 (5.3)	13.8 (4.2)
Modified trail (lines/min)	13.1 (13.9)	15.1 (14.4)	8.5 (11.4)	14.4 (13.1)	13.0 (13.1)
Language					
WAB speech language fluency (10)	7.4 (2.7)†	9.1 (0.7)	8.0 (1.6)	9.4 (1.4)	8.4 (2.0)
MSE apraxia of speech (7 = max)	2.4 (2.3)*†	0 (0)	1.4 (1.7)	0 (0)	1.0 (1.8)
MSE dysarthria rate (7 = max)	1.2 (2.1)	0 (0)	0 (0)	0.2 (0)	0.4 (1.3)
WAB Auditory comprehension (60)	57.6 (2.6)	55.7 (8.6)	59.0 (3.0)	58.3 (3.2)	57.6 (4.7)
WAB word recognition total (60)	59.2 (1.5)	51.2 (9.8)†‡§	58.8 (1.3)	58.8 (1.6)	56.8 (6.2)
WAB repetition total (100)	84.1 (16.2)	91.5 (8.4)	78.0 (18.5)	93.2 (11.8)	87.1 (14.8)
Single word repetition (14)	13.5 (0.8)	13.7 (0.6)	14.0 (0)	14.0 (0)	13.8 (0.6)
Sentence repetition (86)	70.8 (15.7)	77.7 (8.5)	64.0 (18.5)	79.2 (11.8)	73.4 (14.6)
WAB sequential commands (80)	71.5 (9.1)	74.5 (7.2)	69.6 (11.7)	72.7 (9.8)	72.2 (9.2)
Abbreviated BNT (15)	12.2 (2.5)	2.8 (3.4)*†‡	9.0 (2.8)	12.0 (3.3)	8.7 (4.9)

*$P < 0.05$ vs. SD.
†$P < 0.05$ vs. Other dementias.
‡$P < 0.05$ vs. PNFA.
§$P < 0.05$ vs. LPA.
CVLT-MS, California Verbal Learning Test; MMSE, Mini-Mental State Examination; MSE, motor speech evaluation.

impairment). Confrontation naming was tested using a shortened, 15-item version of the BNT.[39] Patients were required to name line drawings of high-frequency and low-frequency objects. The total number of items named correctly, either spontaneously or after a semantic stimulus cue (verbal description of the object, eg, "'grows in the garden'" for "flower"), was used for the imaging analysis. Repetition was assessed using single words and phrases from the WAB Repetition subtest[18] (eg, "Snowman", "Sixty-two and a half," "The telephone is ringing," "The pastry cook was elated"). Sentence comprehension was evaluated using the WAB Sequential Commands subtest[18] that includes a variety of sentences with different length (from "Raise your hands" to "Put the pen on top of the book then give it to me") and which requires comprehension of prepositions (eg, "Point with the pen to the book," "Point with the book to the pen"). The WAB Spontaneous Speech fluency subtest[18] was used to measure language fluency in language production. The test is based on 6 basic questions (eg, "What is your name?," "What is your address?," "Why you are here today?") and on the oral description of the picnic scene. The scores are assigned on the basis of a combination of motor speech function, grammar, and paraphasias (eg, 0 = no words or short, meaningless utterances; 5 = often telegraphic, but more fluent speech with some grammatical organization; 10 = sentences of normal length and complexity, without definite slowing, halting, or articulatory difficulty). This test, therefore, provides a general measure of language fluency and cannot distinguish between the grammatical and articulatory components. We did not consider the "information content" portion of the WAB Spontaneous Speech section that formally deals with comprehension and semantics. The scores of each WAB subtest were entered in the imaging analysis.

Analysis of variance or the Kruskal-Wallis nonparametric test were used to determine overall group differences. Scheffe and Mann-Whitney tests were used for the post hoc analysis.

Imaging Analysis

MRI scans were obtained with a 1.5-T Magnetom VISION system (Siemens, Iselin, NJ). A volumetric magnetization prepared rapid gradient-echo MRI (MPRAGE, TR/TE/TI = 10/4/300 ms) was used to obtain T1-weighted images of the entire brain, 15-degree flip angle, coronal orientation perpendicular to the double spin-echo sequence, $1.0 \times 1.0\,mm^2$ in-plane resolution, and 1.5-mm slab thickness.

VBM included 2 steps: spatial preprocessing (normalization, segmentation, Jacobian modulation, and smoothing) and statistical analysis. Both steps were implemented in the SPM2 software package[40] running on Matlab.[41]

MRI images were preprocessed following the standard procedures of the optimized VBM technique to improve spatial normalization and segmentation.[42] Age and sex-matched template and a priori images were created by averaging 30 age-matched normal control scans that had been normalized and segmented in the MNI (Montreal Neurological Institute) stereotactic space. Images were segmented, normalized, modulated, and finally smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel.

All subjects were entered as a single group into a covariate-only statistical model. Note that performance for each clinical group is provided in Table 1 for completeness, but this was not used in the neuroimaging analysis.

Four separate analyses were conducted in which total scores for naming, repetition, sentence comprehension, and language fluency were entered as covariates of interest. In each analysis, images were proportionally scaled by total gray matter; age and sex were used as nuisance variables. In each analysis, the main effect of the 4 cognitive tasks was tested using a (+1) t-contrast, assuming that higher scores on the cognitive task would be associated with increased gray matter volumes.

On the basis of previous work, we restricted our analyses to the language and semantic memory network that have been previously implicated in PPA (Refs. 17, 43 for review). This region of interest (ROI) included the left perisylvian region and the temporal lobes. The ROI was drawn using the AAL Brain Atlas[44] and was applied to the SPM dataset WFU Pick Atlas[45] (http://www.ansir.wfubmc.edu/download.htm).

Within this ROI, we accepted a level of significance of $P < 0.001$ uncorrected for multiple comparisons in all 4 analyses.

We evaluated the correspondence between observed and predicted brain volumes by calculating multiple R^2 and prediction errors (prediction errors are defined as the average squared deviation between the observed and the fitted volumes).[46] We calculated prediction error using leave-one-out cross-validation[46] and software in the R package.[47]

RESULTS

Cognitive and Functional Data

Demographic information and performance on neuropsychologic measures for each patient group is presented in Table 1. The diagnostic groups did not differ with regard to sex, age at evaluation, disease duration, or Mini-Mental State Examination score. SD group was significantly more impaired in the BNT performance compared with PNFA, LPA, and the other dementias groups [$F(3,47)$ 3.41; $P = 0.025$; Scheffe test: SD vs. PNFA $P = 0.000$, SD vs. LPA $P = 0.001$, SD vs. other dementias $P = 0.000$]. LPA group showed a trend of greater impairment in the WAB Repetition Subtest than SD and other dementias [$F(3,47)$ 2.86; $P = 0.047$, Scheffe test LPA vs. PNFA $P = 0.76$, LPA vs. SD $P = 0.16$, LPA vs. other dementias $P = 0.10$]. PNFA patients were significantly more affected in the WAB language fluency subtest than the other dementias group [$F(3,47)$ 30.25; $P = 0.0001$; Scheffe test $P = 0.03$]. On the contrary, the 4 groups did not differ on WAB Repetition Subtest [$F(3,47)$ 2.86; $P = 0.047$, Scheffe test LPA vs. PNFA $P = 0.76$, LPA vs. SD $P = 0.16$, LPA vs. other dementias $P = 0.10$] and Sequential Commands [$F(3,47)$ 0.59; $P = 0.63$].

Imaging Data

Impaired confrontation naming correlated with gray matter atrophy in the inferior temporal gyri (BA 20/37), fusiform gyri (BA 20/37), temporal poles (BA 21/38), and hippocampi bilaterally, and also the left parahyppocampal gyrus (BA 28) and middle temporal gyrus (BA 20/21) ($P < 0.05$, family-wise error (FWE) corrected; Table 2 and Fig. 1). The highest peaks were localized in the left inferior temporal and left fusiform gyrus.

When considering the total score on the repetition task, no significant correlation was found. A further analysis was performed considering only performance in sentence repetition, because sentences place greater demands on short-term phonologic memory resources than single words.[48–50] When considering only scores for the sentence repetition task, lower scores correlated with atrophy in the posterior portion of left superior temporal gyrus and sulcus (BA 22, $P < 0.001$, uncorrected; Table 2 and Fig. 1).

Lower performance on the sentence comprehension task correlated significantly with greater gray matter volume loss in the dorsal portions of the left middle frontal (BA 44/45, $P < 0.05$, FWE corrected; Table 2 and Fig. 1) and inferior frontal (BA 44) gyri. The left middle temporal (BA 39) gyrus was also correlated with impaired sentence comprehension, although at a lower level of significance ($P < 0.001$, uncorrected; Table 2 and Fig. 1).

Lower performance on the language fluency task was associated with decreased gray matter volume in the more ventral portion of the left middle frontal gyrus (BA 9) ($P < 0.05$, FWE corrected). In addition, left superior (BA 10) and inferior frontal (BA 45) gyri were also correlated with language fluency ($P < 0.001$, uncorrected; Table 2 and Fig. 1).

The results of the statistical analysis showed that with regard to confrontation naming, the R^2 of 0.53 and prediction error of 0.0024 indicated a close correspondence between observed and predicted volumes. Same results for the sentence comprehension analysis with the R^2 of 0.58 and prediction error of 0.0006. On the other hand, in the repetition analysis, the R^2 was 0.26 and the prediction error value was 0.0028, which indicated a weaker correspondence between observed and predicted volumes. Similar results were found for the language

TABLE 2. Results of the VBM Analysis Illustrating Localization of Voxel That Correlated With Each of the 4 Cognitive Tasks

Brain region (BA)	H	*x*	*y*	*z*	T	Z
Confrontation naming						
Inferior temporal gyrus (20/37)	L	−43	−32	−19	8.1	6.4*
	L	−45	−15	−33	7.9	6.3*
	L	−57	−9	−31	7.4	6.0*
	L	−32	−9	−41	7.4	6.0*
	L	−51	−46	−24	6.9	5.7*
	L	−37	−12	−38	7.3	6.0*
	L	−47	−41	−24	7.0	5.8*
	L	−40	−25	−16	7.1	5.8*
	L	−44	−3	−41	7.0	5.8*
	R	39	4	−43	6.4	5.4*
Fusiform gyrus (37/20)	L	−36	−16	−33	7.4	6.0*
	R	35	−7	−45	7.2	5.8*
	L	−30	−33	−22	5.9	5.1*
	R	40	−19	−29	6.1	5.2*
Middle temporal gyrus (21/20)	L	−50	−31	−16	7.2	5.9*
	L	−54	−20	−20	6.5	5.5*
	L	−42	−5	−20	7.4	6.0*
Hippocampus	L	−13	−9	−22	5.9	5.1*
Parahyppocampal gyrus (28)	L	−18	−7	−25	5.7	5.0*
Temporal pole (20/21/36/38)	L	−46	3	−21	6.8	5.7*
	L	−32	5	−36	5.3	4.7*
	L	−41	10	−39	5.2	4.6*
	R	41	−9	−39	6.8	5.6*
	R	41	7	−24	5.4	4.8*
	R	48	7	−19	5.3	4.6*
	R	43	10	−26	5.5	4.8*
Sentence repetition						
Superior temporal gyrus (22)	L	−63	−29	12	3.6	3.3
	L	−55	−35	8	3.5	3.2
	L	−43	−35	14	3.5	3.3
	L	−45	−51	13	3.4	3.3
Sentence comprehension						
Middle frontal gyrus (44/45)	L	−51	25	34	6.1	5.2*
		−48	17	39	4.4	4.0
Inferior frontal gyrus (45)	L	−49	44	18	4.0	3.7
Middle temporal gyrus (39)	L	−55	−69	22	3.7	3.5
Language fluency						
Middle frontal gyrus (9/45)	L	−37	31	51	5.0	4.5*
	L	−51	32	32	3.7	3.4
Inferior frontal gyrus (45)	L	−54	42	13	4.2	3.9
	L	−41	27	4	3.7	3.5
Superior frontal gyrus (10)	L	−32	61	20	4.1	3.8

*$P < 0.05$, FWE corrected for multiple comparison.
H indicates hemisphere; L, left; R, right.

fluency analysis, with an R^2 of 0.36 and prediction error of 0.0038.

DISCUSSION

The differential diagnosis of progressive aphasia at the bedside remains problematic. Anatomically targeted bedside cognitive measures can be a useful tool for localizing brain damage to areas characteristically affected in neurodegenerative diseases. The present study showed that performance on 4 simple language tasks correlated with distinct patterns of regional atrophy in progressive aphasia owing to neurodegeneration: naming ability correlated with temporal volumes, sentence repetition with left superior temporal volumes, sentence comprehension with left dorso-frontal volumes, and language fluency correlated with left ventro-frontal volumes. Further statistical analyses showed that our imaging models accurately predicted the region of atrophy in this population. We compare our anatomic findings with previous data on aphasia owing to stroke and discuss their relevance in relation to the differential diagnosis of PPA.

Atrophy in a widespread region of the temporal lobes, including the poles and the lateral portion of left inferior and middle temporal gyri correlated significantly with confrontation naming scores. This is consistent with previous findings in SD, which is characterized by severe naming deficits and temporal lobe atrophy.[11,21,25,37,51] The same results would not have been predicted by classic literature on aphasia owing to stroke, in which naming deficits are associated with lesion of the perisylvian cortex, including posterior temporal and inferior frontal regions.[52] Our results indicate that, in our cohort of progressive aphasia patients, a naming deficit is most likely associated with temporal dysfunction: the anterior regions could support processing items with shared and correlated features such as living stimuli[53,54] while the lateral areas could be involved in general semantic processing[54] and/or lexical retrieval.[25]

No region's volume correlated with total scores in repetition or with scores in the repetition of single words. This might be due to the fact that our group of patients did not show single word repetition deficits. However, the volume of the posterior portion of the left superior temporal lobe showed correlation with performance in repetition of sentences. Infarction of the posterior, superior temporal region is clinically associated with the acute clinical picture of Wernicke's type of aphasia.[55,56] It is also frequently found in chronic conduction aphasia where repetition deficits are the hallmark of the disorder.[57–60] Modern studies have implicated this area in phonemic processing of speech production and perception,[61,62] and specifically to phonologic storage.[63,64] Patients with PPA also show a repetition deficit.[6] In fact, a sentence repetition deficit is the typical feature of the LPA variant of PPA.[11] Results from the present study show that sentence, and not single word repetition performance, correlates with posterior superior left temporal involvement in progressive aphasia.

The left middle frontal and inferior frontal gyri (pars opercularis and triangularis of Broca's area) significantly correlated with sentence comprehension and language fluency skills; however, the former was associated with a more dorsal region whereas the latter with ventral areas. In addition, infarction of both of middle and inferior frontal regions, together with other neighboring regions, leads to the syndrome of Broca aphasia.[32,65,66] It is worth noting that the language presentation in vascular aphasias and progressive aphasia differ in some aspects, even when similar brain regions are damaged. For example, telegraphic speech and frankly agrammatic production output are rare in the early phase of PNFA,[67,68] though typical in Broca aphasia.[69,70]

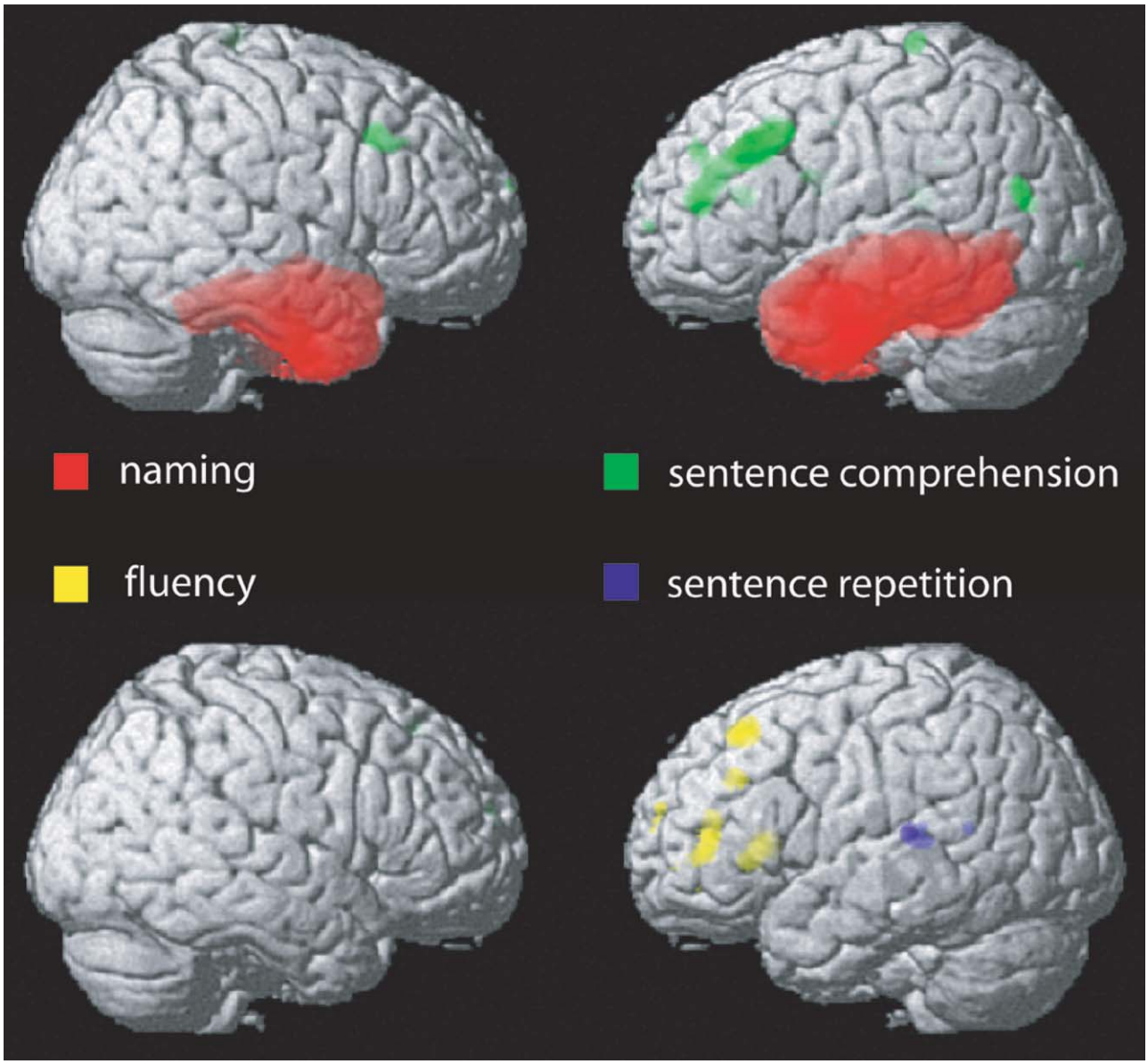

FIGURE 1. Results of the VBM analysis. Upper row: main effects of shortened BNT (red, naming) and WAB sequential commands (green, sentence comprehension). Lower row: main effects of WAB language fluency (yellow, language fluency) and WAB sentence repetition (blue, sentence repetition). Results are superimposed on the 3-dimensional rendering of the Montreal Neurological Institute standard brain and displayed at a threshold of $P<0.001$ uncorrected.

Our data support the view that the left inferior and middle frontal gyri are involved in sentence comprehension.[29,71–77] The anatomic overlap between regions that correlated with language fluency and sentence comprehension is not surprising because the WAB language fluency test also involves judgment of "agrammatism" in language production (eg, to achieve a perfect score, the production of grammatically correct sentences is required). The language fluency results also support the notion that the left inferior frontal gyrus, together with the premotor cortex, basal ganglia and anterior insula compose the network of brain regions that support motor speech in both stroke and neurodegenerative disease.[11,12,30,31,78,79] In our cohort, all patients with PNFA were by definition nonfluent; 11 out of 15 had apraxia of speech and 6 also had dysarthria. All but one had difficulty with comprehension of syntactically complex sentences. It is also worth noticing that poor performance on the WAB fluency subtest cannot differentiate motor speech and grammar impairment. Furthermore, the questions of this task are basic and the objects in the pictures are mostly high familiar objects (eg, radio, tree, etc). For these reasons, often SD patients score at ceiling in this task.

PPA was initially described as a unitary syndrome.[9] More recently, different clinical variants have been described showing specific clinical and MRI patterns of impairment.[11,24,36,80] In the covariate analysis reported in this paper, all patients were entered as a single variable, without a priori classification into different PPA variants. Nevertheless, the areas that correlated with scores in the considered language tests corresponded well to the areas previously described as typically affected in each PPA variant. Anterior temporal atrophy has been consistently associated with SD[21,81,82]; left temporoparietal junction with LPA[11] and left frontal with PNFA.[11,12,23,79] Therefore, different patterns of impairment on the language tests used in this experiment might point to anatomic damage in regions that have previously been associated with the different variants of PPA, and thus might be helpful in the differential diagnosis of this syndrome.

A caveat of the study is that performance on the language tasks was in most cases evaluated by a single clinician, who is certified as speech pathologist (J.O.); however, recordings of controversial cases were reviewed by all clinicians in the language group (S.A., M.L.G.T., J.O., and N.D.) and a consensus was reached. In addition, the VBM technique has some well-known limitations such as limited spatial resolution and possible registration errors. Lastly, some of the results of the correlation analyses could be associated with a specific test because of secondary features of the task; for example, the correlation of parahippocampal/hippocampal gyrus with the naming task might be related to the failure to connect the object to an autobiographical memory.[83] The left hippocampal/parahippocampal atrophy found in our study is consistent with previous work.[84,85]

In conclusion, we demonstrated that performance in 4 simple language tasks is correlated with specific sites of atrophy in progressive aphasia owing to neurodegenerative disorders. Most regions corresponded to those previously identified in vascular aphasic patients. However, a specific role of the anterior temporal lobe in confrontation naming is detected in patients with neurodegenerative disease, in whom this region is more often involved. Performance in naming, sentence repetition, sentence comprehension, and language fluency correlated with atrophy in regions that are differentially involved in each PPA variant and might be useful in the differential diagnosis of this controversial clinical syndrome.

REFERENCES

1. Croot K, Hodges JR, Patterson K. Evidence for impaired sentence comprehension in early Alzheimer's disease. *J Int Neuropsychol Soc*. 1999;5:393–404.
2. Grossman M, D'Esposito M, Hughes E, et al. Language comprehension profiles in Alzheimer's disease, multi-infarct dementia, and frontotemporal degeneration. *Neurology*. 1996;47:183–189.
3. Graham NL, Bak T, Patterson K, et al. Language function and dysfunction in corticobasal degeneration. *Neurology*. 2003;61: 493–499.
4. Frattali CM, Grafman J, Patronas N, et al. Language disturbances in corticobasal degeneration. *Neurology*. 2000;54:990–992.
5. Lindau M, Almkvist O, Kushi J, et al. First symptoms—frontotemporal dementia versus Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2000;11:286–293.
6. Mendez MF, Clark DG, Shapira JS, et al. Speech and language in progressive nonfluent aphasia compared with early Alzheimer's disease. *Neurology*. 2003;61:1108–1113.
7. Galton CJ, Patterson K, Xuereb JH, et al. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain*. 2000; 123(Pt 3):484–498.
8. Josephs KA, Boeve BF, Duffy JR, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. *Neurocase*. 2005;11:283–296.
9. Mesulam MM. Slowly progressive aphasia without generalized dementia. *Ann Neurol*. 1982;11:592–598.
10. Davies RR, Hodges JR, Kril JJ, et al. The pathological basis of semantic dementia. *Brain*. 2005;128(Pt 9):1984–1995.
11. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 2004;55:335–346.
12. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain*. 2006;129(Pt 6):1385–1398.
13. Knibb JA, Xuereb JH, Patterson K, et al. Clinical and pathological characterization of progressive aphasia. *Ann Neurol*. 2006;59: 156–165.
14. Rabinovici GD, Furst A, Miller BL, et al. [11C] PIB PET in Three Variants of Primary Progressive Aphasia. In: 59th Annual Meeting of the American Academy of Neurology; 2006; Boston, 2006.
15. Broca P. Nouvelle observation d'aphémie produite par une lésion de la troisième circonvolution frontale. *Bulletins de la Société d'anatomie*. 1861;2e serie:398–407.
16. Broca P. Perte de la parole: ramollissement chronique et destruction partielle du lobe anterieur gauche du cerveau. *Bulletins de la Societe d'anthropologie*. 1861;1ere serie:235–238.
17. Price CJ. Functional-imaging studies of the 19th Century neurological model of language. *Rev Neurol (Paris)*. 2001;157(8–9 Pt 1): 833–836.
18. Kertesz A. *Western Aphasia Battery*. London, Ontario: University of Western Ontario Press; 1980.
19. Shewan CM, Kertesz A. Reliability and validity characteristics of the Western Aphasia Battery (WAB). *J Speech Hear Disord*. 1980;45:308–324.
20. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. 2nd ed. Philadelphia: Lea & Febiger; 1983.
21. Rosen HJ, Gorno-Tempini ML, Goldman WP, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*. 2002;58:198–208.
22. Mesulam MM. Primary progressive aphasia. *Ann Neurol*. 2001;49: 425–432.
23. Turner RS, Kenyon LC, Trojanowski JQ, et al. Clinical, neuroimaging, and pathologic features of progressive nonfluent aphasia. *Ann Neurol*. 1996;39:166–173.
24. Hodges JR, Patterson K. Nonfluent progressive aphasia and semantic dementia: a comparative neuropsychological study. *J Int Neuropsychol Soc*. 1996;2:511–524.
25. Grossman M, McMillan C, Moore P, et al. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain*. 2004;127(Pt 3):628–649.
26. Ravizza SM, Delgado MR, Chein JM, et al. Functional dissociations within the inferior parietal cortex in verbal working memory. *Neuroimage*. 2004;22:562–573.
27. Bartha L, Benke T. Acute conduction aphasia: an analysis of 20 cases. *Brain Lang*. 2003;85:93–108.
28. Cooke A, Zurif EB, DeVita C, et al. Neural basis for sentence comprehension: grammatical and short-term memory components. *Hum Brain Mapp*. 2002;15:80–94.

29. Just MA, Carpenter PA, Keller TA, et al. Brain activation modulated by sentence comprehension. *Science*. 1996;274: 114–116.
30. Dronkers NF. A new brain region for coordinating speech articulation. *Nature*. 1996;384:159–161.
31. Hillis AE, Work M, Barker P, et al. Re-examining the brain regions crucial for orchestrating speech articulation. *Brain*. 2004;127: 1479–1487.
32. Mohr JP, Pessin MS, Finkelstein S, et al. Broca aphasia: pathologic and clinical. *Neurology*. 1978;28:311–324.
33. Litvan I. Progressive supranuclear palsy and corticobasal degeneration. *Baillieres Clin Neurol*. 1997;6:167–185.
34. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34: 939–944.
35. Mesulam MM. Primary progressive aphasia—differentiation from Alzheimer's disease. *Ann Neurol*. 1987;22:533–534.
36. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51:1546–1554.
37. Hodges JR, Patterson K, Oxbury S, et al. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain*. 1992;115(Pt 6):1783–1806.
38. Kramer JH, Jurik J, Sha SJ, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cogn Behav Neurol*. 2003;16:211–218.
39. Mack WJ, Freed DM, Williams BW, et al. Boston Naming Test: shortened versions for use in Alzheimer's disease. *J Gerontol*. 1992;47:P154–P158.
40. *Statistical Parametric Mapping* [program]. Version 2. London: Wellcome Department Cognitive Neurology.
41. *MATLAB* [program]. Version 7.0.0. Natick, MA: MathWork.
42. Good CD, Scahill RI, Fox NC, et al. Automatic differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. *Neuroimage*. 2002;17:29–46.
43. Price CJ. The anatomy of language: contributions from functional neuroimaging. *J Anat*. 2000;197(Pt 3):335–359.
44. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15:273–289.
45. Maldjian JA, Laurienti PJ, Kraft RA, et al. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of FMRI data sets. *Neuroimage*. 2003;19:1233–1239.
46. Efron B, Tibshirani RJ. *An introduction to the Bootstrap*. New York: Chapman and Hall; 1993.
47. Team RDC. R: A language and environment for statistical computing [serial online]. Available.
48. McCarthy RA, Warrington EK. The double dissociation of short-term memory for lists and sentences. Evidence from aphasia. *Brain*. 1987;110(Pt 6):1545–1563.
49. Martin N, Saffran EM. Repetition and verbal STM in transcortical sensory aphasia: a case study. *Brain Lang*. 1990;39:254–288.
50. Small JA, Kemper S, Lyons K. Sentence repetition and processing resources in Alzheimer's disease. *Brain Lang*. 2000;75:232–258.
51. Boxer AL, Rankin KP, Miller BL, et al. Cinguloparietal atrophy distinguishes Alzheimer disease from semantic dementia. *Arch Neurol*. 2003;60:949–956.
52. Jefferies E, Lambon Ralph MA. Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain*. 2006;129(Pt 8):2132–2147.
53. Brambati SM, Myers D, Wilson A, et al. The anatomy of category-specific object naming in neurodegenerative diseases. *J Cogn Neurosci*. 2006;18:1644–1653.
54. Noppeney U, Patterson K, Tyler LK, et al. Temporal lobe lesions and semantic impairment: a comparison of herpes simplex virus encephalitis and semantic dementia. *Brain*. 2007;130(Pt 4):1138–1147.
55. Kertesz A, Lau WK, Polk M. The structural determinants of recovery in Wernicke's aphasia. *Brain Lang*. 1993;44:153–164.
56. Wernicke C. *Der Aphasische Symptomkomplex*. Breslau: Khon and Neigart; 1874.
57. Anderson JM, Gilmore R, Roper S, et al. Conduction aphasia and the arcuate fasciculus: a reexamination of the Wernicke-Geschwind model. *Brain Lang*. 1999;70:1–12.
58. Quigg M, Fountain NB. Conduction aphasia elicited by stimulation of the left posterior superior temporal gyrus. *J Neurol Neurosurg Psychiatry*. 1999;66:393–396.
59. Selnes OA, Knopman DS, Niccum N, et al. The critical role of Wernicke's area in sentence repetition. *Ann Neurol*. 1985;17: 549–557.
60. Damasio H, Damasio AR. The anatomical basis of conduction aphasia. *Brain*. 1980;103:337–350.
61. Hickok G, Erhard P, Kassubek J, et al. A functional magnetic resonance imaging study of the role of left posterior superior temporal gyrus in speech production: implications for the explanation of conduction aphasia. *Neurosci Lett*. 2000;287: 156–160.
62. Zatorre RJ, Evans AC, Meyer E, et al. Lateralization of phonetic and pitch discrimination in speech processing. *Science*. 1992;256: 846–849.
63. Baddeley A, Hitch G. Working memory. In: Bower GH, ed. *The Psychology of Learning and Motivation*. San Diego: Academic Press; 1974:47–90.
64. Buchsbaum BR, Olsen RK, Koch P, et al. Human dorsal and ventral auditory streams subserve rehearsal-based and echoic processes during verbal working memory. *Neuron*. 2005;48: 687–697.
65. Damasio AR. Signs of Aphasia. In: Sarno MT, ed. *Acquired Aphasia*. New York: Academic Press; 1998:25–40.
66. Metter EJ, Kempler D, Jackson CA, et al. Cerebellar glucose metabolism in chronic aphasia. *Neurology*. 1987;37:1599–1606.
67. Graham NL, Patterson K, Hodges JR. When more yields less: speaking and writing deficits in nonfluent progressive aphasia. *Neurocase*. 2004;10:141–155.
68. Grossman M, Ash S. Primary progressive aphasia: a review. *Neurocase*. 2004;10:3–18.
69. Nespoulous J-L, Dordain M, Perron C, et al. Agrammatism in sentence production without comprehension deficits: reduced availability of syntactic structures and/or of grammatical morphemes? A case study. *Brain Lang*. 1988;33:273–295.
70. Grodzinsky Y. The neurology of syntax: language use without Broca's area. *Behav Brain Sci*. 2000;23:1–21. Discussion 21–71.
71. Caplan D, Waters G, Alpert N. Effects of age and speed of processing on rCBF correlates of syntactic processing in sentence comprehension. *Hum Brain Mapp*. 2003;19:112–131.
72. Cooke A, DeVita C, Gee J, et al. Neural basis for sentence comprehension deficits in frontotemporal dementia. *Brain Lang*. 2003;85:211–221.
73. Dronkers NF, Wilkins DP, Van Valin RD Jr, et al. Lesion analysis of the brain areas involved in language comprehension. *Cognition*. 2004;92:145–177.
74. Friederici AD, Ruschemeyer SA, Hahne A, et al. The role of left inferior frontal and superior temporal cortex in sentence comprehension: localizing syntactic and semantic processes. *Cereb Cortex*. 2003;13:170–177.
75. Keller TA, Carpenter PA, Just MA. The neural bases of sentence comprehension: a fMRI examination of syntactic and lexical processing. *Cereb Cortex*. 2001;11:223–237.
76. Michael EB, Keller TA, Carpenter PA, et al. fMRI investigation of sentence comprehension by eye and by ear: modality fingerprints on cognitive processes. *Hum Brain Mapp*. 2001;13:239–252.
77. Stowe LA, Broere CA, Paans AM, et al. Localizing components of a complex task: sentence processing and working memory. *Neuroreport*. 1998;9:2995–2999.
78. Gorno-Tempini ML, Ogar JM, Brambati SM, et al. Anatomical correlates of early mutism in progressive nonfluent aphasia. *Neurology*. 2006;67:1849–1851.
79. Nestor PJ, Graham NL, Fryer TD, et al. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain*. 2003;126(Pt 11):2406–2418.

80. Kertesz A, Davidson W, McCabe P, et al. Primary progressive aphasia: diagnosis, varieties, evolution. *J Int Neuropsychol Soc*. 2003;9:710–719.
81. Mummery CJ, Patterson K, Price CJ, et al. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol*. 2000; 47:36–45.
82. Williams GB, Nestor PJ, Hodges JR. Neural correlates of semantic and behavioural deficits in frontotemporal dementia. *Neuroimage*. 2005;24:1042–1051.
83. Gardini S, Cornoldi C, De Beni R, et al. Left mediotemporal structures mediate the retrieval of episodic autobiographical mental images. *Neuroimage*. 2006;30:645–655.
84. Chan D, Fox NC, Scahill RI, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol*. 2001;49:433–442.
85. Barnes J, Whitwell JL, Frost C, et al. Measurements of the amygdala and hippocampus in pathologically confirmed Alzheimer disease and frontotemporal lobar degeneration. *Arch Neurol*. 2006;63:1434–1439.

