Primary Progressive Aphasia (PPA) is a behaviorally focal dementia syndrome characterized by the insidious onset and gradual progression of deficits that can involve any aspect of language, including word finding, object naming, fluency, syntax, and word comprehension. The initial symptoms occur in the absence of major deficits in other cognitive domains, particularly memory, for at least the first 2 years after onset.\(^1\)\(^-\)\(^4\) Although isolated cases of progressive language dissolution had been described in the late 19th and early 20th centuries,\(^5\)\(^-\)\(^9\) the first report focusing on a series of patients with slowly progressive aphasia was published in 1982 and led to the subsequent delineation of the primary progressive aphasia (PPA) syndrome.\(^1\)\(^,\)\(^4\)

Patients with PPA can have a fluent or nonfluent aphasia and can display variable deficits of language comprehension. The related term "semantic dementia" has been used to denote a type of progressive aphasia characterized by preserved fluency and impaired language comprehension. Semantic dementia is also occasionally accompanied by visual face and object recognition deficits such as prosopagnosia.\(^10\)\(^-\)\(^13\) When free of face and object recognition deficits, semantic dementia constitutes a subtype of PPA with poor comprehension of verbal semantics. The patients in this study had intact comprehension of conversational speech and therefore represent a PPA clinical subtype distinct from semantic dementia.

Neuropathological reports in nearly 50 patients with PPA have identified abnormalities in frontal, perisylvian, and temporal cortices.\(^2\)\(^,\)\(^14\)\(^-\)\(^16\) Approximately 60% of patients have shown nonspecific focal atrophy, also known as neuronal loss with gliosis lacking in distinctive histopathological features.\(^2\) Fewer than 20% show the pathology of Alzheimer's disease. Some of these patients have an unusual perisylvian and temporal neocortical distribution of neurofibrillary tangles, which occasionally spares medial temporal lobe structures.\(^17\) Another 20% show the tau-positive, intracytoplasmic bodies of Pick's disease.\(^18\) In patients without Alzheimer's disease pathology, PPA can be considered one of the focal variants of frontotemporal dementia.

Computerized tomography and magnetic resonance imaging (MRI) of the brain have largely corroborated

Primary Progressive Aphasia: PPA and the Language Network

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Primary Progressive Aphasia (PPA) is a behaviorally focal dementia syndrome with deterioration of language functions but relative preservation of other cognitive domains for at least the first two years of disease. In this study, PPA patients with impaired word finding but intact comprehension of conversational speech and their matched control subjects were examined using voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI). fMRI compared signal changes during phonological and semantic language tasks with those during a control task (matching letters). PPA patients showed longer reaction times and reduced accuracy versus controls on the language tasks, but no performance differences on the control task. VBM demonstrated reduced gray matter in left superior temporal and inferior parietal regions in the PPA group. However, these patients showed a normal pattern of activation within the classical language regions. In addition, PPA patients showed activations, not seen in normals, in fusiform gyrus, precentral gyrus, and intra-parietal sulcus. These activations were found to correlate negatively with measures of naming and task performance. The additional activations in PPA may therefore represent a compensatory spread of language-related neural activity or a failure to suppress activity in areas normally inhibited during language tasks.

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the flocality of anatomical involvement and have shown predominant atrophy in the left lateral temporal lobe (superior, middle, and inferior gyri) in patients with PPA.\textsuperscript{19–21} Moreover, positron emission tomography (PET) and single-photon emission computerized tomography in patients with PPA have shown resting-state deficits in cortical metabolism and blood flow in left anterior and posterior perisylvian regions.\textsuperscript{2,22–24} Although some right-sided abnormalities have been found in a few cases, the metabolic state of the right hemisphere generally has been within normal limits in these studies. Thus, resting functional imaging data have largely reflected the clinical flocality of PPA.

To date, few functional neuroimaging studies have been performed with PPA patients. Grabowski and colleagues performed an \textsuperscript{15}O-PET imaging study in a single patient with PPA, who showed abnormal activation in the left middle frontal and inferotemporal regions, and deactivations in the right hemisphere.\textsuperscript{25} Another \textsuperscript{15}O-PET study compared normal subjects with four patients with progressive fluent aphasia and poor comprehension (ie, semantic dementia). This study demonstrated decreased activity in the left posterior inferior temporal gyrus and increased activity in left premotor, left anterior superior temporal, and right temporoparietal areas during the pyramids-and-palm trees test of visual semantic categorization.\textsuperscript{26} The regions of functional abnormality were anatomically distinct from anterolateral temporal areas that showed decreased gray matter density as estimated by voxel-based morphometry (VBM) in the same patients. These findings led to the hypothesis that semantic dementia may reflect a disruption of functional connectivity involving the posterior inferior temporal lobe, and that this disruption could even include areas showing minimal atrophy.\textsuperscript{26,27}

PPA and its variants provide a unique opportunity to study how the language network changes in response to an apparently focal and slowly progressive disease process. This report is based on a sample of PPA patients with impaired word finding but preserved comprehension of conversational speech. Preliminary results on a subset of these patients have been reported in abstract form.\textsuperscript{28} The specific aims of this study were to determine how this subtype of PPA alters the functional anatomy of language networks, whether the functional changes are distinct from areas of cortical atrophy, and whether these two markers of PPA are related to language abilities.

**Subjects and Methods**

**Subjects**

Fourteen patients (mean age, \(64 \pm 6.6\) years; 8 men, 6 women) who fulfilled the diagnostic criteria for PPA.\textsuperscript{4} (Table 1) and who demonstrated relatively intact verbal comprehension on clinical examination were recruited for this study.

The clinical impression of intact comprehension was based on the patient’s ability to comprehend conversational speech and intact comprehension of object names during formal testing. Patients were additionally classified as fluent or nonfluent. The designation of “nonfluent” reflected the presence of one or more of the following criteria: (1) reduced number of words expressed per minute, (2) decreased phrase length, or (3) frequent word-finding pauses either in spontaneous speech output or on the Oral Cookie Theft subtest of the Boston Diagnostic Aphasia Examination (BDAE).\textsuperscript{29} Fourteen older normal control subjects (mean age, \(63 \pm 8.6\); 8 men, 6 women) with no history of significant medical, neurological, or psychiatric illness also were recruited. All subjects were right-handed as assessed by the modified Edinburgh inventory\textsuperscript{30} with an average handedness score of +95 ± 7.75 for the PPA subjects and +90 ±14.4 for the normal subjects (\(p > 0.05\)). All subjects specified English as their first language. Informed consent was obtained from all subjects, and the study protocols were approved by the Institutional Review Board at Northwestern University.

**Neuropsychological Testing**

Most of the PPA patients, as well as most of the controls, underwent neuropsychological testing within 6 months of scanning for characterization of their cognitive functioning in a variety of domains including attention, language, memory, comportment, executive, and visuospatial functions. A subset of the following neuropsychological batteries were administered to each subject: language measures: Western Aphasia Battery,\textsuperscript{31} Boston Diagnostic Aphasia Examination (selected subtests),\textsuperscript{29} Boston Naming Test (BNT),\textsuperscript{32} nonlan-

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Criteria for PPA (Mesulam)\textsuperscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Insidious onset and gradual progression of word-finding, object-naming, or word comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological testing of language.</td>
</tr>
<tr>
<td>2. All limitation of daily living activities can be attributed to the language impairment, for at least 2 years after onset.</td>
</tr>
<tr>
<td>3. Intact premorbid language functions (except for developmental dyslexia).</td>
</tr>
<tr>
<td>4. Absence of significant aphatic, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits, or sensorimotor dysfunction within the initial 2 years of illness. This criterion can be fulfilled by history, survey of daily living activities, or formal neuropsychological testing.</td>
</tr>
<tr>
<td>5. Calculia and ideomotor apraxia can be present even in the first 2 years. Mild constructional deficits and perseveration (eg, as assessed by the go no-go task) are also acceptable as long as neither visuospatial deficits nor disinhibition influence daily living activities.</td>
</tr>
<tr>
<td>6. Other domains may become affected after the first 2 years, but language remains the most impaired function throughout the course of the illness and deteriorates faster than other affected domains.</td>
</tr>
<tr>
<td>7. Absence of “specific” causes such as stroke or tumor as ascertained by diagnostic neuroimaging.</td>
</tr>
</tbody>
</table>

PPA = primary progressive aphasia.
Behavioral Tasks

All participants performed two tasks, identical in design and time course, while undergoing fMRI. During the active condition of both tasks, subjects were presented visually with pairs of words and were asked to make a judgment about these words (Fig 1). In the phonological task (HOM), subjects viewed a pair of words and pushed a button only if the words were homonyms (i.e., had identical pronunciation but dissimilar orthography and meaning). In the semantic task (SYN), subjects responded only if the words in a pair were synonyms (i.e., had a very similar meaning but dissimilar orthography and phonology). The words presented in the two tasks were obtained from the on-line Oxford Psycholinguistic Database and were controlled for length (four to seven characters) and a Kucera–Francis frequency of 10 to 500.

For the reference control condition in both tasks (STRINGS), subjects were presented with pairs of all-consonant letter strings of the same average length as the words in the active task and were asked to respond if the letter strings were identical. Subjects responded in all cases by pressing a response button held in their right hand. Reaction times were recorded for all responses. Task accuracy was determined from the percentage of correct behaviors, that is, (no. of hits + no. of correct rejections)/total no. of stimuli.

The tasks followed a block design and consisted of eight blocks each of the control and active conditions presented alternately. The stimuli were presented every 5,505 milliseconds, and individual blocks lasted 30 seconds. Stimuli were presented and responses were collected using Superlab software (Cedrus, San Pedro, CA) running on a Power Macintosh computer (Apple, Cupertino, CA). The stimuli were projected onto a custom-designed nonmagnetic rear-projection screen using a Proxima active matrix liquid crystal display projector (San Diego, CA). Subjects viewed the screen, located approximately 170 cm from their eyes, through a nonmagnetic mirror.

Subjects went through an initial training period on abbreviated versions of the two tasks while outside the scanner. Ultimate inclusion of subjects in the group analysis was dependent on relatively intact language comprehension and above-chance performance (≥62.5% accuracy, 24/40 correct), on each of the three conditions during the actual experimental session. Accuracy estimates were based on the binomial test. These criteria were met by 10 of the 14 subjects for the homonym task and by 11 subjects for the synonym task. The remaining PPA patients were excluded from analysis, giving a final group size of 10 patients for the HOM task analysis and 11 patients for the SYN task analysis. The control group for both tasks contained 11 cognitively intact individuals chosen to match the overall group of 11 PPA patients for age, gender, and education (Table 2).

Functional Magnetic Resonance Imaging

Subjects were imaged using a 1.5T Siemens Vision scanner (Erlangen, Germany). The subjects’ heads were immobilized using a vacuum pillow (VacFix, Bionix, Toledo, OH) in addition to the restraint calipers built into the head coil, to minimize head movements during the scanning procedure.41 Laterality for image processing was indicated using a vitamin E capsule taped to the left temporal region.

Single-shot echo planar images were obtained in 32 slices parallel to the anterior commissure-posterior commissure (AC-PC) line according to parameters in our previous studies for block-designed tasks: TR/TE, 4,350/40 milliseconds; flip angle, 90 degrees; field of view, 240 mm; matrix, 64 × 64; and slice thickness, 4 mm.42 At the beginning of each functional run, the MR signal was allowed to equilibrate over four scans, which were excluded from analysis. In addition, high-resolution, T1-weighted anatomical images were acquired using a three-dimensional fast low-angle shot sequence (TR/TE, 22/5.6 milliseconds; flip angle, 25 degrees; field of view, 256 mm; matrix, 256 × 256; slice thickness, 1 mm). A saturation band was located inferior to the imaging volume to

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Table 2. Subject Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>PPA Group (n = 11)</th>
<th>Normal Group (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.4 ± 4.6</td>
<td>66.5 ± 6.7</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>5:6</td>
<td>5:6</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>16.5 ± 3.4</td>
<td>16.0 ± 1.9</td>
</tr>
<tr>
<td>Mean disease duration (yr)</td>
<td>3.0 ± 1.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Handedness</td>
<td>95.9 ± 7.4</td>
<td>96.8 ± 6.4</td>
</tr>
</tbody>
</table>

PPA = primary progressive aphasia; n/a = not applicable.
null the signal from the arteries and reduce pulsation artifacts in the temporal lobes. The final voxel size was 1 mm$^3$.

**Functional Magnetic Resonance Data Analysis**

fMRI data were analyzed on UNIX/Linux workstations under the Matlab software environment (Mathworks, Sherborn, MA) using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm).\(^{43-46}\) All functional images were time acquisition corrected to the slice obtained at 50% of the TR. The images were realigned to the functional scan immediately preceding the anatomical T1 image. All images (anatomical and functional) were normalized to the Montreal Neurological Institute (MNI-305) template, which approximates the anatomical space delineated by Talairach and Tournoux.\(^{47}\) Functional images then were smoothed with a 10 mm full width half maximal isotropic Gaussian kernel for inclusion in the group analyses.

Condition-specific effects at each voxel were estimated using the general linear model.\(^{44}\) Linear contrasts were set up to test for voxelwise effects of signal differences between the active and control conditions, and SPM(t) maps were calculated for individual subjects. Within-group and intergroup comparisons were performed using a random effects model to account for the effects of intersubject variability. The random effects analysis was performed by first generating parameter effects images for each contrast within a subject. For example, in the SYN task, a parameter effect image of SYN versus STRINGS was generated for each PPA patient or normal subject. These images then were entered into second-level analyses using one-sample t tests for effects within groups, and two-sample t tests for effects between groups. Significance was assigned to the resulting t-fields using the theory of Gaussian random fields.\(^{44,46}\) The random effects SPM(t) maps were thresholded at a $p$ value less than or equal to 0.001 uncorrected, and activations were considered significant at a $p$ value of less than or equal to 0.05 after correction for multiple comparisons across the volume. Additional analyses included simple regression analyses, which tested for correlations of activation with reaction times or accuracy for each of the subject groups.

To test for possible relationships between the patients’ clinical fluency subtype and the functional or structural imaging results, we designated PPA patients as fluent or nonfluent (by two neurologists, D.R.G. and M.-M.M.) on the basis of the clinical neurological examination. The examiners were blinded to the subjects’ MRI results when rating them. The patients’ fluency status then was used as a covariate in an analysis. Other analyses included simple regression to examine the relationship between activations and language test performance as estimated by the PPA patients’ score on the BNT. The BNT was chosen because all subjects received this test (see Table 4).

In addition to the whole-brain analyses specified above, the described correlation and regression analyses were performed on the areas identified as active by the intergroup comparisons for each language task. These regions of interest (ROI) analyses were performed to reduce the impact of multiple comparisons on the calculation of significance for these regions. The use of regions defined by the intergroup contrasts was valid because the correlational and regression analyses were orthogonal to these contrasts.

**Masked Analyses**

To assess whether intergroup comparisons were significant because of increased activity in the PPA group or decreased activity in the normal group, we inclusively masked the analyses comparing both groups by the respective main effects. Masking analysis ensures that the results at least reflect the presence of a positive simple main effect. For example, results from the intergroup homonym contrast (PPA$_{\text{HOM}}$ − PPA$_{\text{STRINGS}}$) − (NL$_{\text{HOM}}$ − NL$_{\text{STRINGS}}$) were masked by PPA$_{\text{HOM}}$ − PPA$_{\text{STRINGS}}$. This analysis therefore displays regions that showed greater activation in the PPA than in the normal group and had to be present in the PPA$_{\text{HOM}}$ − PPA$_{\text{STRINGS}}$ comparison. Thus, the activation could not just reflect deactivations in the NL$_{\text{HOM}}$ − NL$_{\text{STRINGS}}$ contrast. A second analysis masked (NL$_{\text{STRINGS}}$ − NL$_{\text{HOM}}$) − (PPA$_{\text{STRINGS}}$ − PPA$_{\text{HOM}}$) by (NL$_{\text{STRINGS}}$ − NL$_{\text{HOM}}$). This analysis showed areas that were significantly deactivated in the normal group. Similar analyses were performed for the synonym task. In all cases, the functional image determining the mask was thresholded at a $p$ value of less than 0.05 uncorrected. Note that the masking procedure does not affect the final statistics, which always used a significance level of $p$ or equal to less than 0.05 corrected.\(^{48}\)

**Plot of Parameter Estimates**

To further examine the fMRI response for each task in each group, we extracted and compared the parameter estimates from the voxels showing significant differences between groups from each of the individual subjects. The parameter estimates provide a measure of the fMRI response for each contrast (eg, HOM $-$ STRINGS or SYN $-$ STRINGS). Because SPM99 normalizes the signal to a value of 100, the response is proportional to percentage signal change between active and control conditions and can be compared within and between subject groups.

**Voxel-based Morphometry**

The T1-weighted structural MRI scans were preprocessed by normalization to the MNI-305 template, followed by segmentation of gray and white matter.\(^{49-51}\) The gray matter image segments were multiplied by the Jacobian determinants of the deformation fields that were defined during normalization. This step has the effect of transforming gray matter per unit volume in normalized space into a density measure in native space and essentially conserves the amount of gray matter before and after normalization (ie, gray matter is not added if there is regional stretching of the brain, or lost if it is compressed).\(^{50}\) Segmented gray matter images were smoothed with a 12 mm isotropic Gaussian kernel and analyzed at each voxel for changes in gray matter density in PPA patients relative to the controls, as an indirect measure of neuronal loss. A confound for global signal was included in this analysis so that inferences pertain to regionally specific effects and not global measures of atrophy. Significance was assigned to the resulting t-fields using the theory of Gaussian random fields,\(^{44,46}\) and the resulting statistical map was thresholded at $p$ values less than or equal to 0.001 uncor-
Results

Neurological Examination

The neurological examination in all patients showed word-finding and naming deficits and variable degrees of dysgraphia. Comprehension was relatively preserved in conversation, although 8 of 11 patients had difficulty comprehending grammatically complex sentences with embedded clauses. A subset of the patients (8 of 11) was nonfluent, as reflected by decreased phrase length, frequent word-finding pauses either in sponta-
neous speech output or on the Oral Cookie Theft subtest of the Boston Diagnostic Aphasia Examination, or a decreased number of words per minute in conversation. Three of the patients were largely fluent, showing relatively preserved phrase length and flow, and infrequent word-finding pauses (Table 3).

Neuropsychological Testing
PPA patients showed impairments on some tests of language, for example, BNT and verbal fluency (lexical and categorical). However, these patients performed within normal limits on auditory verbal comprehension subtests taken from either the Western Aphasia Battery or the Boston Diagnostic Aphasia Examination. Some patients also showed impairments on neuropsychological tests that required verbal comprehension or response (eg, Mini-Mental Status Exam, CERAD Word Lists, CERAD Logical Memory I & II [recall]). However, a clinical review of daily living activities and knowledge of current events for each patient did not provide evidence for any impairment of episodic memory. In addition, when verbally mediated tests were adapted to reduce the need for a spoken response, subjects displayed preserved retention of information. Therefore, the low scores on some nonlanguage tests were attributed to interference from the language impairment. PPA patients showed less impairment in CERAD Word List recognition, Visual Target Cancellation, Judgment of Line Orientation, and Visual-Verbal, representing tests of memory, visuospatial functions, and reasoning and executive functions, respectively. Normal controls showed no impairments on any of the neuropsychological tests. Scores on a subset of the language and nonlanguage neuropsychological tests for both groups are shown in Table 4.

Task Performance
Patients with PPA (n = 10 for HOM and n = 11 for SYN) showed significantly increased reaction times when compared with the normal control group (n = 11) for both phonological (HOM; PPAHOM = 2,209 ± 360 milliseconds vs NLHOM = 1,714 ± 423 milliseconds; p < 0.05) and semantic (SYN; PPA SYN = 2,596 ± 430 milliseconds vs NL SYN = 1,792 ± 513 milliseconds; p < 0.001) tasks. Accuracy also was reduced significantly for PPAs on both phonological (PPAHOM = 0.84 ± 0.11 vs NL HOM = 0.96 ± 0.04; p < 0.05) and semantic (PPASYN = 0.87 ± 0.11 vs NL SYN = 0.97 ± 0.03; p < 0.01) tasks compared with normal subjects. However, scores were significantly greater than chance for all patients.

On the letter strings control task, reaction times were comparable for the two groups (PPASTR = 2,746 ± 326 milliseconds vs NLSTR = 2,678 ± 411 milliseconds; p = 0.05). Accuracy on the control task

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Table 4. Neuropsychological Scores for PPA and Normal Subject Groups

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Age/Gender</th>
<th>WAB or BDAE (% correct)*</th>
<th>BNT (60)</th>
<th>Category Fluency (animals)</th>
<th>Lexical Fluency (FAS)</th>
<th>MMSE (30)</th>
<th>Word List Recog. (10)</th>
<th>Trails A (secs)</th>
<th>JLO (% correct)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>69/F</td>
<td>96</td>
<td>52</td>
<td>13</td>
<td>23</td>
<td>27</td>
<td>10</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>62/M</td>
<td>87</td>
<td>55</td>
<td>15</td>
<td>30</td>
<td>17</td>
<td>20</td>
<td>10</td>
<td>n/a</td>
<td>87</td>
</tr>
<tr>
<td>67/F</td>
<td>94.40</td>
<td>22</td>
<td>8</td>
<td>17</td>
<td>12</td>
<td>25</td>
<td>10</td>
<td>n/a</td>
<td>73</td>
</tr>
<tr>
<td>57/M</td>
<td>80.50</td>
<td>9</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>26</td>
<td>10</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>59/M</td>
<td>100</td>
<td>36</td>
<td>18</td>
<td>12</td>
<td>12</td>
<td>23</td>
<td>10</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>67/M</td>
<td>86.10</td>
<td>31</td>
<td>11</td>
<td>21</td>
<td>11</td>
<td>21</td>
<td>10</td>
<td>47</td>
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<tr>
<td>67/M</td>
<td>100</td>
<td>55</td>
<td>15</td>
<td>17</td>
<td>11</td>
<td>n/a</td>
<td>n/a</td>
<td>46</td>
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</tr>
<tr>
<td>58/F</td>
<td>84.50</td>
<td>51</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td>22</td>
<td>10</td>
<td>35</td>
<td>73</td>
</tr>
<tr>
<td>65/F</td>
<td>96.50</td>
<td>34</td>
<td>8</td>
<td>8</td>
<td>12</td>
<td>28</td>
<td>10</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>71/F</td>
<td>96</td>
<td>53</td>
<td>14</td>
<td>17</td>
<td>13</td>
<td>30</td>
<td>10</td>
<td>46</td>
<td>87</td>
</tr>
<tr>
<td>65/F</td>
<td>100</td>
<td>55</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>-</td>
<td>58 ± 2.4</td>
<td>24.2 ± 3.4</td>
<td>45.4 ± 7.4</td>
</tr>
</tbody>
</table>

NL (n = 9), mean ± SD

*Underlined scores were from the BDAE, others from the WAB. Boldface scores are greater than 1 SD from the mean score for normal subjects.

*Normal data not available.

PPA = primary progressive aphasia; WAB = Western Aphasia Battery (auditory comprehension); BDAE = Boston Diagnostic Aphasia Examination–auditory comprehension (indicated by underlines in row one); BNT = Boston Naming Test, MMSE = Mini-Mental Status Exam; Word List Recog. = CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) Word List Recognition; Trails A = Trailmaking Test A; JLO = Judgment of Line Orientation; n/a = not available at time of scanning.
was slightly reduced for the PPA group relative to the normal group (PPASTR/H11005 0.97 ± 0.04 vs NLSTR/H11005 0.99 ± 0.02; p < 0.05). However, PPA patients were significantly more accurate on the STRINGS task than on either of the language tasks (p ≤ 0.05 vs each task). Reaction times and accuracy for the two groups on all three tasks are shown in Figure 2.

**Voxel-Based Morphometry Results**

Analysis of gray matter density of the structural MRIs showed an area of reduced gray matter in PPA patients (n = 11) compared with normal subjects (n = 11) spanning the posterior perisylvian temporal and inferior parietal lobes (Fig 3a). Voxels with significantly reduced gray matter for the group of PPA patients compared with controls were found in the left inferior parietal lobule, and in the left superior temporal gyrus. An examination of gray matter density in these regions for each of the individual subjects is shown in Figure 4.

The fluent and nonfluent PPA groups showed somewhat different patterns of atrophy when compared with controls. The nonfluent patients showed inferoparietal and dorsolateral prefrontal cortex reduced gray matter (xyz = −62 −42 27, p = 0.002; xyz = −50 −46 48, p = 0.003; and xyz = −49 11 50, p = 0.003), whereas fluent patients showed nonsignificant superior temporal gray matter reduction (xyz = −70 −19 4; p = 0.11). However, there was no significant difference in the pattern of atrophy when directly comparing the nonfluent and fluent PPA groups.

ROI analyses of fluency, based on the areas listed in Table 5, showed a trend toward reduced gray matter in nonfluent compared with fluent subjects in the more superior and medial of the inferior parietal lobule foci (xyz = −62 −43 37; p = 0.061; see Fig 4). Simple regression analysis of BNT scores versus whole-brain gray matter density showed no significant correlation between naming deficit and atrophy. Moreover, none of the three regions in the inferior parietal lobule or superior temporal gyrus (see Table 5) was found to significantly correlate with BNT on ROI analysis.

**Functional Magnetic Resonance Imaging Results:**

**Homonym versus Letter Strings**

For the homonym task relative to the control task (HOM − STRINGS), both PPA patient (n = 10) and control (n = 11) subject groups activated a common network of areas, including the “classic” left perisylvian frontal and temporal language areas. These activations included the left inferior frontal gyrus (ie, Broca’s area, broadly defined as including BA 44/45/46), left posterior middle temporal gyrus (ie, Wernicke’s area − BA 22/37), and the anterior cingulate gyrus (BA 32). The PPA patient group showed an additional activation in the left middle frontal gyrus. Phonological activations for both groups are shown in Figure 3b and c and listed in Table 6.

**Synonym versus Letter Strings**

For the synonym task relative to the control task (SYN − STRINGS), activations in the control group (n = 11) included bilateral inferior frontal gyri (BA 44/45), bilateral superior temporal sulci (BA 21/22), and the left temporoparietal junction. Activations not quite meeting threshold were seen in the left anterior cingulate gyrus and right insula (see Fig 3d and Table 6).

The PPA group (n = 11) appeared to activate a subset of the regions seen in the normal group for the SYN − STRINGS contrast. These regions were bilateral inferior frontal gyri (BA 44/45), anterior cingulate gyrus (BA 32), left intraparietal sulcus, and right insula. The left posterior superior temporal sulcus was
Fig 3. Voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) results. (a) VBM results showing significant gray matter density decreases for the primary progressive aphasia (PPA) group in the left superior temporal gyrus and left inferior parietal lobule (iPL). Representative fMRI activations: (b) normal group homonym task (HOM; n = 11), (c) PPA HOM (n = 10), (d) normal synonym (SYN; n = 11), (e) PPA SYN (n = 11). The cerebellar activation is not pictured. Areas of significant activation for PPA > control in (f) phonology (HOM) and (g) semantics (SYN) include intraparietal sulcus (iPS), fusiform gyrus (Fus), and precentral gyrus (pCG). No areas of significant activation for control > PPA were present for either task. iFG = inferior frontal gyrus; mFG = middle frontal gyrus; mTG = posterior middle temporal gyrus; aCG = anterior cingulate gyrus; TPJ = temporoparietal junction; iPS = intraparietal sulcus; sTS = superior temporal sulcus; sTG = superior temporal gyrus; Lt = left; Rt = right; Thal = thalamus; Ins = insula; pCG = posterior cingulate gyrus.
The control subjects showed no areas of significantly increased activation relative to the PPA patient group, although one focus in the left temporoparietal junction (xyz = −42 −63 18) showed a trend toward significance for the synonym task (p = 0.07).

Masking the intergroup contrasts provided information about signal increases or decreases in each group. Masking the HOM − STRINGS contrast (PPA_{HOM} − PPA_{STRINGS}) − (NL_{HOM} − NL_{STRINGS}) by PPA_{HOM} − PPA_{STRINGS} showed that PPA patients significantly activated the right fusiform gyrus. Masking the same contrast by NL_{STRINGS} − NL_{HOM} showed that normal subjects significantly deactivated the right fusiform gyrus and left intraparietal sulcus. For the accordingly masked SYN − STRINGS contrast, the only areas significantly activated in PPA patients were right fusiform gyrus and left precentral gyrus, whereas areas significantly deactivated in the normal subjects included right fusiform gyrus, left intraparietal sulcus, and right precentral gyrus.

The plot of parameter estimates, shown in Figure 5, demonstrates that both subject groups showed task-related activations in Broca’s and Wernicke’s areas; that is, the parameter estimates were consistent with greater activation for the language tasks (HOM or SYN) versus the control task (STRINGS). The situation was quite different in the areas that differentiated PPA and controls. In these areas, the normal subjects displayed deactivations when language tasks were compared with letter strings, whereas PPA patients showed relative activations. Neither whole-brain analyses nor region of interest analyses in areas of significant intergroup difference showed any effect for fluency on activation increases for either of the tasks. However, in a ROI analysis, signal in right fusiform regions for HOM − STRINGS and SYN − STRINGS showed significant inverse correlation with BNT (r = −0.57 and −0.64, respectively; p < 0.05 after correction for multiple comparisons), as did signal in right precentral gyrus for the SYN − STRINGS contrast (r = −0.70; p < 0.05). Signal in left intraparietal sulcus showed a trend toward inverse correlation with BNT (r = −0.51; p = 0.055). Plots of signal in these regions for the individual subjects versus BNT score are shown in Figure 6. Linear regressions between signal in each of the areas showing anomalous activations in PPA (dependent variable) and task performance (independent variable) showed different relationships between PPA patients and normal control subjects (Fig 7). Activity in right fusiform gyrus in the HOM > STRINGS contrast was...
were found. All activated regions in the PPA group and performance on the synonym task. No other correlations between anomalously increased signal in left precentral gyrus for the primary progressive aphasia; iFG = inferior frontal gyrus; mFG = middle frontal gyrus; mTG = posterior middle temporal gyrus; aCG = anterior cingulate gyrus; TPJ = temporoparietal junction, iPS = intraparietal sulcus, sTS = superior temporal sulcus.

<table>
<thead>
<tr>
<th>Location</th>
<th>HOM—STRINGS</th>
<th>PPA (n = 10)</th>
<th>SYN—STRINGS</th>
<th>PPA (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left iFG</td>
<td>-45 54 -9</td>
<td>3.7e-13</td>
<td>-48 42 -15</td>
<td>0.000</td>
</tr>
<tr>
<td>Left mFG</td>
<td>-42 6 36</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left posterior mTG</td>
<td>-51 -45 0</td>
<td>1.4e-05</td>
<td>-57 -45 -3</td>
<td>0.002</td>
</tr>
<tr>
<td>Left aCG</td>
<td>-9 51 39</td>
<td>1.8e-06</td>
<td>-3 27 36</td>
<td>0.006</td>
</tr>
<tr>
<td>Right iFG</td>
<td>-39 -12</td>
<td>0.008</td>
<td>-39 33 -15</td>
<td>0.000</td>
</tr>
<tr>
<td>Left TPJ</td>
<td>-39 -60 24</td>
<td>0.000</td>
<td>-42 -69 30</td>
<td>0.036</td>
</tr>
<tr>
<td>Left iPS</td>
<td>-42 -69 30</td>
<td>0.036</td>
<td>-42 -57 42</td>
<td>4.7e-09</td>
</tr>
<tr>
<td>Right iPS</td>
<td>42 33 -15</td>
<td>8.3e-07</td>
<td>57 30 -6</td>
<td>5.8e-05</td>
</tr>
<tr>
<td>Right Insula</td>
<td>45 -9 15</td>
<td>0.193</td>
<td>39 -15 6</td>
<td>0.003</td>
</tr>
<tr>
<td>Bilateral sTS</td>
<td>-45 -27 0</td>
<td>0.007</td>
<td>-57 -39 0</td>
<td>0.551</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>51 -24 -3</td>
<td>4.0e-10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Activations are significant at \( p \leq 0.05 \) corrected, unless italicized. PPA = primary progressive aphasia; iFG = inferior frontal gyrus; mFG = middle frontal gyrus; mTG = posterior middle temporal gyrus; aCG = anterior cingulate gyrus; TPJ = temporoparietal junction, iPS = intraparietal sulcus, sTS = superior temporal sulcus.

Table 7. Coordinates for Regions of Significant Difference between the PPA and Control Groups for Each Task

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates (XYZmm)</th>
<th>( p ) corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOM (PPA-NL) Right fusiform gyrus</td>
<td>30 -54 -21</td>
<td>0.005</td>
</tr>
<tr>
<td>Left intraparietal sulcus</td>
<td>-27 -57 51</td>
<td>0.020</td>
</tr>
<tr>
<td>Right intraparietal sulcus</td>
<td>39 -51 60</td>
<td>0.056</td>
</tr>
<tr>
<td>SYN (PPA-NL) Left precentral gyrus</td>
<td>-54 3 15</td>
<td>0.011</td>
</tr>
<tr>
<td>Right precentral gyrus</td>
<td>51 3 21</td>
<td>0.035</td>
</tr>
<tr>
<td>Right fusiform gyrus</td>
<td>27 -69 -18</td>
<td>0.001</td>
</tr>
<tr>
<td>Left intraparietal sulcus</td>
<td>-27 -60 54</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Activations are significant at \( p \leq 0.05 \) corrected, unless italicized. PPA = primary progressive aphasia.

found to predict both reaction time and task accuracy on the HOM task only for the PPA subject group, with increased activity correlated with longer reaction times and reduced accuracy (\( p = 0.023 \) and 0.025, respectively).

Increased signal in left precentral gyrus for the SYN > STRINGS contrast was found to be associated with reduced task accuracy on the SYN task (\( p = 0.038 \), again, only for the PPA group (Fig 8). No significant relationships were found between signal and task performance in the normal control group for either task. No other correlations between anomalously activated regions in the PPA group and performance were found. All \( p \) values were corrected for multiple comparisons across the correlations.

Discussion

This report examines the neuroanatomical and functional substrates of PPA in a group of patients with word-finding deficits and relatively preserved comprehension. The neural substrates for language alterations in this group of PPA patients with its particular constellation of clinical features were studied using behavioral measures, VBM, and fMRI. Statistical comparisons were made using random effects analyses, which account for intersubject variance. This type of analysis is less susceptible to the presence of outliers. Thus, the findings represent effects over the group of PPA patients as a whole. The relative homogeneity of the findings also was demonstrated by examining the parameter estimates for the PPA and normal groups for both the VBM and functional activation results (see Figs 4 and 5).

We found that the PPA patients were slower and less accurate than normal subjects in the language-related portions of the tasks but performed nearly equivalently to normal subjects on a demanding control task. Therefore, we propose that the changes in activation that we observed in the PPA patients appear to reflect specific changes in language function rather than any generalized slowing of behavior or an inability to understand the task requirements. Although our group of PPA patients demonstrated relatively intact comprehension for conversational speech on clinical testing, they were impaired on the synonym task, a task that is quite challenging because of its rapid pace and lack of contextual cues.

VBM demonstrated areas of significant gray matter density reduction for the group of PPA patients in the superior temporal gyrus and the inferior parietal lobule in the left hemisphere (see Figs 3a and 4). This pattern
is consistent with previous computerized tomography and MRI studies of atrophy in PPA. However, the pattern is distinct from that reported in VBM studies of semantic dementia, in which the combination of fluent aphasia and comprehension deficits were associated with bilateral temporopolar and inferofrontal atrophy. We did not observe significant effects of fluent versus nonfluent patient subtype or naming deficit severity on the whole-brain or ROI-based morphometric analyses of PPAs or controls. However, the absence of a significant clinical–anatomical relationship in this study may have reflected the low power to detect such a relationship given the relatively small sample size of each patient fluency subgroup (n = 3 for fluent and n = 8 for nonfluent).

During fMRI, language-related activations in the normal subject group were consistent with those reported in the literature. For the phonological (HOM) task, these activations included left-sided inferior frontal and posterior temporal regions within the traditional boundaries of “Broca’s” and “Wernicke’s” areas and surrounding regions, as well as the anterior cingulate gyrus. These areas have been implicated previously in phonological analysis, and response selection. The semantic processing task additionally demonstrated left-sided inferior parietal and left anterior temporal activations, as well as right-sided activations in inferior frontal, anterior insular, and superior temporal regions, areas that have been implicated in accessing word meaning.

Despite their somewhat reduced performance on the language tasks, the PPA subject group activated very similar left hemisphere areas as the normal subjects in both tasks. Contrary to expectations, PPA-related fMRI abnormalities also were detected outside of the canonical language areas and took the form of excessive rather than diminished activations, as determined by masking with the relevant language task versus letter string contrast (see Fig 3f and g). In the homonym task versus letter string contrast, the PPA group showed greater activation than the normal group in the left intraparietal sulcus and right fusiform gyrus, whereas in the synonym task versus letter string contrast, the PPA group showed greater activation in bilateral precentral gyri, left intraparietal sulcus, and right fusiform gyrus. This combination of findings deviates notably from language-related functional imaging findings in semantic dementia. In that disorder, bilateral temporopolar atrophy was associated with significantly reduced activity in regions distant to the areas of atrophy. However, the two patient groups (PPA patients in this study and those with semantic dementia) differ fundamentally from each other in that the progressive aphasia patients had minimal deficits in single-word comprehension, whereas impaired comprehension is a hallmark feature of semantic dementia. One similarity in the activations for the semantic task in this study and the one used by Mummery and colleagues (1999) is that both patient groups showed abnormally increased activity in left precentral gyrus. The aberrant activations shown in Figure 3 are based on contrasting the PPA with the normal group. The areas of abnormality therefore represent either excessive neuronal recruitment or defective inhibition in the PPA group. Furthermore, either possibility could arise from an abnormal neural response to either the language task or to the letter-string control task. The latter possibility (ie,
that the PPA-related differences result from aberrant responses to the letter strings task) is unlikely because PPA patients demonstrated intact performance, comparable to that of the normal subject group, in the letter-string task. However, this alternative explanation needs to be addressed more directly with the help of event-related task designs. The distribution of neuronal activity in response to a cognitive task, including language, reflects a complex pattern of excitations and inhibitions. Figure 5 indicates that normal subjects showed deactivations in areas where PPA subjects had aberrant task-related activity. Thus, the abnormality in PPA appears to represent a failure to inhibit activations outside of the language network in a task-related manner. This abnormality could reflect either impaired inhibitory control emanating from the atrophic areas or from the compensatory recruitment of additional areas due to dysfunction within the language network. Note that the classic language areas responded to language tasks with nearly equivalent activations in both PPA patients and normal subjects (see Fig 4). Moreover, increased activity in nonlanguage regions appeared to correlate with longer reaction times and reduced task accuracy for the PPA subject group, but not for the normal control group (see Figs 7 and 8). These results may indicate that the functional involvement of these regions did not enhance performance in the tasks, and that activity in these regions might potentially interfere with language processing and task performance. Activity in nonlanguage regions furthermore was related to increased naming deficit severity (see Fig 6), illustrating the relevance of abnormal fMRI activations to clinical features of the aphasia. Functional activation in posterior parietal regions is seen primarily in attentional tasks, including tasks of verbal working memory. The increased activation in the left intraparietal sulcus in PPA therefore could also reflect increased task-related attentional or working memory demands arising from the decreased efficiency of the language network. In normal subjects, word reading is a highly learned, automatic task. In PPA, this process may lose its automaticity and may become increasingly more dependent on laborious grapheme-to-phoneme transformations, such as those that are necessary for reading unfamiliar pseudowords.

Fig 6. Boston Naming Test (BNT) score versus regional fMRI response for PPA patients: a) right fusiform gyrus for (HOM - STRINGS), n = 10; and b) right fusiform gyrus, c) right precentral gyrus, and d) left intraparietal sulcus for (SYN - STRINGS) n = 11. PPA patients showed significant relationships between fMRI responses and naming deficit severity in these regions of anomalous activation. $r = \text{Pearson's linear correlation coefficient}; R\text{ Fus} = \text{right fusiform gyrus}; r\text{ prCG} = \text{right precentral gyrus}; L\text{ IPS} = \text{left intraparietal sulcus.}$
Fiez and Petersen suggested that primary motor cortex participates in the transformation from phonological to articulatory representations. Furthermore, activation in left precentral gyrus has been seen in normal subjects and adult dyslexic patients reading pseudowords. Lexical decision tasks involving pseudowords also have shown greater activity in left precentral gyrus than tasks of word reading or feature detection. A recent event-related study of word–pseudoword processing in a lexical decision task has shown activation of the left ventral precentral sulcus for pseudowords when compared with common words. These findings support the contention that the aberrant precentral area of activity seen in PPA may reflect an altered approach to the task so that words require more intensive processing as if they were pseudowords.

In summary, a comparison of word reading to letter string identification tasks showed aberrant activations in PPA at sites that are not typically activated by normal subjects performing the same tasks. The magnitude of these aberrant activations was correlated with task performance during the imaging session as well as with scores on the BNT. These aberrant activation sites could reflect either the emergence of compensatory neuronal strategies for language processing or the disintegration of neuronal pathways, which normally inhibit the spread of neural activity to areas outside of the relevant network. The areas of PPA-related atrophy, mostly confined to the left temporoparietal region, did not show abnormal activations or deactivations in this set of tasks, indicating that the residual neurons in atrophic areas maintain at least some of their premorbid response characteristics.

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