Anterior Temporal Laterality in Primary Progressive Aphasia Shifts to the Right

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In aphasia due to stroke, language-related activity shifts not only to undamaged cortex within the dominant hemisphere but also toward right-sided areas homotopical to the left-sided lesion. We examined whether a rightward shift takes place in primary progressive aphasia (PPA). Nineteen PPA patients participated, 19 healthy subjects and 14 patients with amnestic mild cognitive impairment who served as controls. Subjects underwent neuropsychological assessment, structural magnetic resonance imaging (MRI), and a functional MRI with a factorial design: words versus pictures and associative-semantic versus visuoperceptual task. Measures of neuropsychological performance were entered as regressors into a multiple linear regression analysis, with response amplitude during the associative-semantic versus control conditions as outcome variable. Language competence correlated negatively with responses in the right anterior temporal cortex and positively with volume and responses in the left-sided homotope. In normal subjects, anterior temporal activation was more extensive to the left than the right (laterality index [LI], +0.64; standard error [SE], 0.11). Laterality was inverted in PPA with word comprehension deficit (LI, −0.34; SE, 0.19), with an intermediate pattern in PPA without comprehension deficit (LI, +0.23; SE, 0.14). The rightward laterality shift previously reported in aphasic stroke extends to PPA, in particular, when comprehension is deficient.

Recruitment of the unaffected nondominant hemisphere is a robust finding in language studies after stroke,1–9 along with activity increases in undamaged cortex within the dominant hemisphere.6,10,11 The contralesional activity is localized homotopically to the left-sided perisylvian lesion site.2,4,8,12,13 This phenomenon has been described as a “laterality shift.”5 A similar shift takes place in tumor patients.14,15 We examined whether primary progressive aphasia (PPA), a focal neurodegenerative disorder,16,17 is also associated with a laterality shift.

We combined voxel-based morphometry (VBM) with functional magnetic resonance imaging (fMRI) in PPA patients with or without single-word comprehension deficit.16 We included a healthy as well as a patient control group who fulfilled the Petersen criteria for amnestic mild cognitive impairment (MCI).18 We adapted a classic neuropsychological test of associative semantics, the Pyramids and Palm Trees test (PPT),19–21 for use in fMRI. Compared with visuoperceptual judgments, this task activates a distributed left-hemispheric system that is common for words and pictures.21 Given the focal nature of the symptoms associated with PPA,17 we tested the hypothesis that, in analogy with other focal aphasic disorders,2,4,8,13 PPA would be associated with a shift of activity during the associative-semantic condition toward right-hemispheric areas homotopic to the left-sided areas hit by the disease.

Subjects and Methods

Subjects

Nineteen patients who fulfilled the criteria for PPA16,17 participated, 10 men and 9 women, between 45 and 78 years of age (mean, 68.6; standard deviation [SD], 8.0 years), with a mean education level of 12.3 years (SD, 3.0) and a mean Oldfield score of +85.3.22 One PPA subject (Case 13) was left-handed (Oldfield score −73). Word retrieval problems were the primary reason for attending the memory clinic in all patients. Mean disease duration was 3.79 years (SD, 2.46), mean Boston Naming Test (BNT)23 score 36.2 of 60 (SD, 12.8), and mean Animal Verbal Fluency (AVF) score 12.7 (SD, 5.0). Language assessment comprised the validated Dutch version of the Aachen Aphasic Test (AAT)24 and the verbal associative-semantic task of the validated Dutch version of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA).25,26 In all PPA subjects, the score of at least one language task fell two SDs below the mean of control subjects. An extensive neuropsychological protocol allowed us to exclude significant impairment in cognitive domains other than language in all PPA subjects (Table 1).

Seven of 19 PPA patients (Cases 1–7) scored two SDs...
below the mean of normal controls on the AAT word–picture matching tasks, both in the visual and the auditory modality, as well as on the PALPA verbal association task. This is indicative for a significant word comprehension deficit. These patients were also significantly more impaired on the Object Decision task that than PPA patients without word comprehension problems (see Table 1). These patients fulfilled criteria for semantic dementia according to Lund–Manchester criteria. Mean disease duration in this subgroup was 3.4 years (SD, 1.9), mean BNT was 26.7 (SD, 12.9), and mean AVF was 10.3 (SD, 2.5).

Conversely, PPA patients without word comprehension deficit (Cases 8–19) were significantly more impaired on the “articulation” and the “syntactic structure” subitems of the AAT than those who had word comprehension problems (see Table 1). The articulation subitem measures articulation, prosody, and speech flow (words per minute). Syntactic structure measures complexity and completeness of a sentence, word order, and usage of inflections and conjugations. These patients fulfilled criteria for nonfluent progressive aphasia according to Lund–Manchester criteria. Mean disease duration in this subgroup was 4.0 years (SD, 2.6), mean BNT was 41.7 (SD, 9.0), and mean AVF was 14.2 (SD, 5.5).

Six PPA patients were receiving antihypertensive therapy and eight were receiving cholesterol-lowering agents. One PPA patient (Case 9) was taking venlafaxine 150mg daily, and two patients (Cases 17, 18) were taking citalopram 20mg daily for remitted depressive symptoms. One patient had a history of coronary events. Two control groups underwent an identical protocol. (1) Nineteen normal controls (10 men, 9 women; mean age, 69.1 [SD, 8.7]; education level, 12.3 years [SD, 2.6]; Oldfield score, +86.7). As in the PPA group, one control subject was left-handed (Oldfield score, −64). Eight subjects were receiving antihypertensive treatment and eight were taking cholesterol-lowering agents. One subject had a history of coronary events. (2) Fourteen patients who fulfilled the criteria for amnestic MCI (8 men, 6 women; mean age, 66.5 [SD, 7.0]; educational level, 12.8 years [SD, 2.7]; Oldfield score,
One subject was left-handed (Oldfield score, −46). Seven MCI patients were receiving antihypertensive treatment and three were taking cholesterol-lowering agents. Two had a history of coronary events.

All subjects gave written informed consent. The study protocol was approved by the Ethical Committee, University Hospital Gasthuisberg, Leuven.

**Functional Magnetic Resonance Imaging Experiment: Stimuli and Tasks**

Stimuli were projected onto a screen 28 cm in front of the subjects’ eyes. The design of the fMRI experiment was factorial (Fig 1) and similar to that of a previous positron emission tomography study in healthy subjects. The first factor, task, had two levels: associative-semantic (see Fig 1A, C) versus visuoperceptual judgment (see Fig 1B, D). The second factor, input modality, also had two levels: pictures (see Fig 1A, B) versus printed words (see Fig 1C, D). The associative semantic condition (see Fig 1A, C) consisted of a modified version of the PPT. During a trial, a triplet of stimuli was presented for 5,250 milliseconds, one stimulus on top (the sample stimulus) and one in each lower quadrant (the test stimuli) (see Fig 1). Subjects had to press a left- or right-hand key depending on which of the two test stimuli matched the sample stimulus more closely in meaning. A given triplet was presented in either the picture or the word format and this was counterbalanced across subjects. In the visuoperceptual control condition (Fig 1B, D), a stimulus was presented in three different sizes. Subjects had to press a left- or right-hand key depending on which of the two test stimuli matched the sample stimulus more closely in size.

**Image Acquisition**

A 1.5-tesla Siemens Sonata system (Siemens Medical Solutions, Erlangen, Germany) equipped with an eight-channel receive-only head coil (MRI Devices, Waukesha, WI) provided a T1-weighted structural volume (coronal inversion recovery prepared three-dimensional gradient-echo images; inversion time 800 milliseconds, TE/TR 3.93/1,950 milliseconds) as well as T2* echo planar images (42 sagittal slices; voxel size 3 × 3 × 3 mm³; TE/TR, 40/3,000 milliseconds). Usage of the GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) method maximized sensitivity for anterior temporal activity changes and minimized susceptibility artefacts. A total of 116 volumes were acquired during each run. Each run consisted of three replications of each of the four conditions. Subjects underwent four to six runs each.

**Image Analysis**

We used Statistical Parametric Mapping 2002. After realignment and normalization, the EPI volumes were spatially smoothed using a 6 mm full-width at half-maximum isotropic Gaussian kernel. A high-pass filter of 216 seconds was applied and a low-pass filter consisting of a canonical hemo-
dynamic response function (HRF). The epoch-related response was modeled by a canonical HRF, convolved with a boxcar. A $t$ statistic for the parameter estimates was generated for each subject for the contrast between associative-semantic minus visuoperceptual conditions for words and pictures together and for the contrasts associative-semantic minus visuoperceptual condition for words or for pictures separately. The individuals’ $t$ maps were transformed to $Z$ maps and entered into a second level analysis.

At second level, we conducted a multiple linear regression analysis with fMRI response amplitude during associative-semantic versus visuoperceptual conditions as dependent variable and individual factor scores as regressors. Individual factor scores express how well a given subject performs on the neuropsychological tests clustered by a given factor. Factors were extracted from the neuropsychological data set of all 52 subjects using the eigenvalue one test (Henry F. Kaiser) and orthogonal rotation (Statistica version 6; Stat-Soft, Tulsa, OK). For each of the factors that had an Eigenvalue higher than 1, we calculated the individual factor scores and entered them into the multiple regression analysis. This procedure is similar to that applied in previous studies of stroke recovery that correlate behavioral data sets with fMRI responses. It offers two advantages. First, the number of regressors is limited to the number of significant factors, usually 3 to 4, extracted in a data-driven manner. Second, orthogonal rotation of factors allows one to remove any colinearity between regressors. We validated our approach against a series of simple linear regression analyses with raw neuropsychological test scores as regressors.

The significance map was thresholded at a voxel-level inference threshold of $p$ value less than 0.05 corrected for the entire brain volume.

**Laterality Index**

In analogy with stroke recovery studies, we calculated a laterality index: from the multiple linear regression group analysis, we selected the voxels of peak activation ($p < 0.05$ corrected) together with all brain voxels within a radius of 10 voxels from this peak, and for each voxel their contralateral counterpart. Within this bilateral volume of interest, we determined for each subject how many voxels were activated to the left and to the right during the associative-semantic versus the visuoperceptual condition at an uncorrected $p < 0.001$. Our laterality index (LI) was defined as: $(L - R)/(L + R)$, with $L$ being the number of voxels activated to the left and $R$ to the right.

**Consistency with Previous Studies**

In analogy with previous studies of PPA, we also conducted comparisons of gray matter volume and brain responses between PPA and controls. Volume was assessed by means of the optimized voxel-based morphometry method.

**Results**

**Neuropsychological Data**

Factor analysis extracted four factors from the neuropsychological data set. The first factor explained 44.6% of the total variance (Eigenvalue, 6.7) and clustered the naming ($r = 0.90$) and comprehension tasks ($r = 0.88$) of the AAT and the PALPA verbal association task ($r = 0.87$). The second factor (Eigenvalue, 2.5) clustered the delayed recall ($r = 0.91$) and recognition ($r = 0.78$) tasks of the Auditory Verbal Learning Test (AVLT). The third factor (Eigenvalue, 1.5) consisted of the Trail Making Test B/A ratio ($r = -0.82$) and the fourth factor (Eigenvalue, 1.1) of the Number Location task ($r = 0.92$).

**Performance of the Functional Magnetic Resonance Imaging Task**

Performance of the fMRI tasks was analyzed by means of a three-factor repeated-measures analysis of variance (ANOVA) with stimulus modality and task as within-subject factors (two levels: pictures vs words and semantic vs visuoperceptual, respectively) and group as between-subject factor (three levels: PPA, MCI, and normal subjects).

There was a main effect of group upon reaction times ($F[2, 49] = 7.1, p < 0.01$), accuracies ($F[2, 49] = 5.1, p < 0.01$) and omissions ($F[2, 49] = 5.2, p < 0.01$; Table 2). Post hoc analysis showed that PPA patients responded more slowly and less accurately than normal subjects ($p < 0.01$) and MCI patients ($p < 0.05$) and made more omissions than normal subjects ($p < 0.01$).

There was a significant interaction between group and task ($F[2, 49] = 6.2, p < 0.01$): PPA patients made significantly more omissions during the semantic task relative to the visuoperceptual task than normal subjects.

Table 2. Reaction Times, Accuracies, and Omissions during the fMRI Experiment, Mean (SE)

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<thead>
<tr>
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<th>Reaction Time (msec)</th>
<th>Accuracy (% correct)</th>
<th>Omissions</th>
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<td>PPA Controls MCI</td>
<td>PPA Controls MCI</td>
<td>PPA Controls MCI</td>
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<tr>
<td>Semantic (P)</td>
<td>3,551 (127) 3,014 (100) 3,077 (129)</td>
<td>67.8 (2.3) 81.0 (1.7) 78.8 (2.2)</td>
<td>15.6 (1.9) 6.2 (1.8) 5.8 (2.1)</td>
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<tr>
<td>Visuoper (P)</td>
<td>2,969 (154) 2,537 (94) 2,702 (147)</td>
<td>80.6 (1.8) 88.9 (1.6) 87.7 (1.8)</td>
<td>6.5 (1.5) 3.3 (1.3) 5.6 (1.6)</td>
</tr>
<tr>
<td>Semantic (W)</td>
<td>3,595 (130) 2,866 (88) 2,965 (113)</td>
<td>75.6 (2.9) 84.2 (2.0) 84.9 (1.9)</td>
<td>12.3 (2.0) 2.9 (1.8) 7.0 (2.2)</td>
</tr>
<tr>
<td>Visuoper (W)</td>
<td>2,813 (117) 2,355 (88) 2,400 (118)</td>
<td>84.4 (3.1) 90.1 (1.9) 88.1 (2.0)</td>
<td>6.3 (1.3) 2.0 (1.2) 4.7 (1.4)</td>
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SE = standard error; PPA = primary progressive aphasia; MCI = mild cognitive impairment; Semantic(P) = associative-semantic task with pictures; Semantic(W) = associative-semantic task with words; Visuoper-etc = visuoperceptual task with pictures; Visuoper(W) = visuoperceptual task with words

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subjects and MCI patients (see Table 2). A similar trend was present for reaction times ($F_{[2,49]} = 2.8$, $p = 0.07$). There were no three-way interactions between group, task, and modality.

**Neuroimaging Results**

**Main Analysis.** The amplitude of right anterior temporal fMRI responses during the associative-semantic conditions compared with the visuoperceptual conditions correlated *inversely* with individual language factor scores ($54, -3, -33, Z = 4.77$, ext. 35, corrected $p < 0.05, r = -0.62$): right anterior temporal responses were stronger as individual language factor scores were lower (Fig 2A, B). In the symmetrical left-sided anterior temporal cortex, the direction of the correlation was opposite: Response amplitude in left anterior temporal cortex was higher as individual language factor scores were better ($-42, 12, -24, Z = 4.17$, ext. 53, uncorrected $p < 0.001, r = 0.53$). Left anterior temporal brain volume also correlated positively with individual language factor scores ($-48, 12, -24, Z = 5.63$, ext. 336, corrected $p < 0.001, r = 0.67$; $-28, -6, -24, Z = 4.93$, ext. 295, corrected $p < 0.05, r = 0.63$; see Fig 2C, D).

Right anterior temporal response amplitude differed between PPA subgroups. It was higher in PPA patients with compared with those without word comprehension deficit ($p < 0.05$; see Fig 2B). Left anterior temporal volume also differed: it was significantly smaller in PPA patients with compared with those without word comprehension deficit ($p < 0.005$; see Fig 2D).

Simple linear regression analyses with raw test scores confirmed these results. Right anterior temporal brain responses correlated negatively with PALPA verbal associative semantic scores ($57, -3, -33, Z = 5.31$, $r = -0.58$, corrected $p < 0.01$) and with AAT naming ($57, -3, -33, Z = 4.63$, $r = -0.60$, uncorrected $p < 0.00001$) and comprehension scores ($54, -3, -33, Z = 4.38$, $r = -0.57$, uncorrected $p < 0.00001$). A trend in the same direction was observed for the Token test ($57, -3, -33, Z = 4.08$, uncorrected $p < 0.001, r = 0.55$) and the Object Decision test ($54, -3, -24, Z = 3.58$, uncorrected $p < 0.001, r = -0.47$). Performance of none of the other neuropsychological tests correlated with right anterior temporal activity ($p > 0.001$).

The laterality index differed significantly between groups (one-way ANOVA, $F_{[3,48]} = 6.4$, $p < 0.005$; see Fig 2E). According to a post hoc analysis, the laterality index differed significantly between PPA with comprehension deficit and healthy controls ($p < 0.0005$), between PPA without word comprehension deficit and healthy controls ($p < 0.05$), between PPA with comprehension deficit and MCI ($p < 0.005$), and between PPA with and without comprehension deficit ($p < 0.05$). In the anterior temporal cortex of normal subjects, the activation during the associative-semantic compared with the visuoperceptual task was more extensive in the left hemisphere ($L = 90.1$ [SE, 18.0]; $R = 20.4$ [SE, 8.2]; LI = 0.64 [SE, 0.11]; see Fig 2E, green). Only in one, left-handed normal control, was the laterality index negative (see Fig 2E). This left-sided preponderance was also true in the MCI group ($L = 82.7$ [SE, 20.6]; R = 38.5. [SE, 12.5]; LI = 0.38 [SE, 0.14]). Conversely, in PPA patients with word comprehension deficits, anterior temporal activation was more extensive to the right ($L = 14.8$ [SE, 29.6]; R = 28.9 [SE, 13.4]; LI = -0.34 [SE, 0.19]; see Fig 2E, red solid). PPA patients without word comprehension deficits showed an intermediate pattern ($L = 61.4$ [SE, 22.7]; R = 35.7 [SE, 22.7]; LI = 0.23 [SE, 0.14]; see Fig 2E, red dashed). The denominator of the laterality index, that is, the total number of activated voxels to the left and to the right, did not differ significantly between groups (one-way ANOVA, $F_{[3,48]} = 0.81$, $p = 0.49$).

To exclude differences in performance during the fMRI session as an explanation, we conducted a multiple linear regression analysis with behavioral performance during the fMRI tasks as regressors and fMRI response as dependent variable. This analysis did not yield any significant effects in left or right anterior temporal areas, even when the threshold was lowered to an uncorrected $p < 0.01$.

**Consistency with Previous Studies**

PPA patients showed lower fMRI responses than controls during the semantic versus the visuoperceptual conditions in left inferior temporal and left fusiform gyrus ($-33, -33, -30$, ext. 90, corrected $p < 0.01$), as in previous studies. $^{37,40}$ PPA patients showed volume loss in the left superior temporal sulcus compared with controls ($-54, -30, -4$, $Z = 3.45$, uncorrected $p < 0.001$). $^{37,38}$

In PPA patients with comprehension deficit, left anterior temporal volume was significantly decreased compared with controls ($-30, -2, -28$, $Z = 4.94$, corrected $p < 0.05$). $^{36,38,39}$ Left anterior temporal volume correlated with naming accuracy ($-42, 20, -42$, $Z = 4.40$, uncorrected $p < 0.001$). $^{39}$

In PPA without comprehension deficit, volume was decreased in the left superior temporal sulcus ($-54, -30, -4$, $Z = 3.22$, uncorrected $p < 0.001$).$^{37,38}$ There was a trend toward a positive correlation between naming accuracy and left frontal ($-26, 42, -18$, $Z = 3.27$, uncorrected $p < 0.001$; $-48, 16, 26$, $Z = 2.85$, uncorrected $p < 0.005$), insular ($-21, -18, 0$, $Z = 2.80$, uncorrected $p < 0.005$) and temporal cortical volumes ($-62, -16, -34$, $Z = 4.29$; $-58, -40, 2$, $Z = 3.32$, uncorrected $p < 0.001$), replicating previous results. $^{39}$
Fig 2. (A) Multiple linear regression analysis testing for negative correlations between language competence and functional magnetic resonance imaging (fMRI) response during associative-semantic versus control conditions (p < 0.05 corrected for the total brain search volume). (B) Regression plot: y axis: fMRI response amplitude during associative semantic versus control conditions in the right anterior temporal cluster of significant activation. x axis: individual language factor scores. (green) Normal controls; (red squares) primary progressive aphasia (PPA) without comprehension deficit; (red diamonds) PPA with comprehension deficit; (blue) mild cognitive impairment (MCI). (C) Multiple linear regression analysis testing for positive correlations between language competence and brain volume (p < 0.05 corrected for the total brain search volume). (D) Regression plot: y axis: gray matter volume in the left anterior temporal cluster of significant atrophy. x axis: Language factor score. Same conventions as in B. (E) Laterality index: extent of right-sided versus left-sided activation (uncorrected p < 0.001) within the anterior temporal volume of interest. Each line corresponds to one subject. x axis: right: right anterior temporal half of the volume of interest; left: left anterior temporal half of the volume of interest. y axis: number of voxels activated either to the left or to the right for a given subject within the volume of interest, divided by the total number of voxels activated bilaterally. (green) Normal controls; (red dashed line) PPA without comprehension deficit; (red solid line) PPA with comprehension deficit; (blue) MCI.
Discussion
In PPA, right anterior temporal response amplitude increases as language abilities decrease (see Fig 2A, B). In the homotopical left-sided region, brain volume and responses decrease in parallel with language competence (see Fig 2C, D). In PPA with comprehension deficit in particular, anterior temporal activation during the associative-semantic compared with the visuo-perceptual task was more extensive to the right than to the left, opposite of what is seen in normal controls (see Fig 2E). The laterality shift resulted from actual activity increases to the right in those patients who were most severely affected and was not exclusively caused by left-sided activity decreases (see Fig 2B).

Differences in fMRI task performance can be excluded as an explanation. The regressors of our analysis were derived from the neuropsychological assessment and not from performance during fMRI scanning. When we entered the performance parameters of the fMRI session into a regression analysis, the correlation remained far below significance. Furthermore, the relationship between language scores and fMRI response went in opposite directions in the two hemispheres. This cannot be attributed to a specific task difficulty effect.

In aphasic stroke patients, a rightward shift of activation correlated inversely with picture naming performance and was associated with poorer recovery than ipsilesional activity increases. The inverse relationship between right-hemispheric activity and language competence in stroke is in accordance with the inverse relationship between right anterior temporal activity and language competence in PPA in our study (see Fig 2B).

Right anterior temporal hyperactivity may reflect compensatory mechanisms, failure to compensate, or changes in task-solving strategies. It may also be maladaptive: Transcallosal disinhibition may result in right-sided activation that does not serve an actual semantic processing purpose. Historically, reports of cases of left-hemispheric stroke who suffered a subsequent right-hemispheric stroke and experienced worsening of aphasia have suggested an active role of the right hemisphere in language processing. In classic studies of recovery after left-hemispheric stroke, lesion size correlated positively with recovery of comprehension and inversely with rates of improvement of word generation or sentence production. These and other studies have led to the hypothesis that the right hemisphere can compensate for word comprehension but not for articulation or grammatical impairment. This lesion-based hypothesis fits with our observation in PPA that the anterior temporal laterality shift occurred primarily in those patients who had a comprehension deficit.

In aphasic stroke or tumor patients, active interference with right-hemispheric activity affects language performance. For instance, TMS above the right inferior frontal zone of activity increased response latency during a verb generation task. Longitudinal interventional studies in PPA are required to determine the effect of similar manipulations upon language performance.

In neurodegenerative diseases, such as PPA, recovery of function is unfortunately rare. Functional brain reorganization nevertheless takes place under such conditions. A recent fMRI study revealed activity increases outside the classic language network in nonfluent progressive aphasia. Our findings differ from this previous report by the confinement of the activity increases to right-hemispheric areas homotopic to focal left-hemispheric areas of structural atrophy.

There was considerable variability between individuals (see Fig 2B, D, E). Decreased left-sided anterior temporal volume and increased right-sided anterior temporal activity were more pronounced in PPA patients who had comprehension deficits compared with those who did not (see Fig 2B red diamonds versus red squares). This difference between the two subgroups is not caused by differences in overall disease severity: Syntactic production and articulation was more impaired in the PPA sample without word comprehension deficit than in the group with word comprehension deficit (see Table 1). The double dissociation between word comprehension and articulatory and grammatical output is a classic feature of the clinical heterogeneity among PPA patients. Our data corroborate the view that this clinical heterogeneity reflects differences in underlying brain substrate.

Our left temporal findings confirmed previous volumetric and functional imaging studies in semantic dementia and nonfluent progressive aphasia. Frontal changes were relatively weak compared with previous studies. Our patients were on average less severely affected than those studied by Grossman and colleagues. Second, heterogeneity within the subgroup of PPA without comprehension deficit may also explain why frontal changes were relatively weak in our study.

Anterior temporal cortex is not a classic perisylvian language area. Until recently, herpes simplex encephalitis and anterior temporal lobectomy were the principal neurological conditions unveiling the critical role of anterior temporal cortex for language and semantic memory. Detailed studies of cognition and anatomy in semantic dementia have drawn attention to the lateral and medial anterior temporal cortex as key structures for the processing of word meaning.

Functional imaging studies of the intact brain have confirmed this view: left anterior temporal cortex is activated during associative-semantic judgements compared with visuo-perceptual judgements regardless of in-
put modality, words, or pictures.\textsuperscript{21} It is activated when subjects read stories compared with sequences of unconnected sentences\textsuperscript{66} or sentences compared with random word sequences.\textsuperscript{67} We propose that the left anterior temporal pole is an associative structure that binds together representations of meaning that are distributed over human cerebral cortex.\textsuperscript{67–69}

In conclusion, functional reorganization of the language system in PPA\textsuperscript{16,17} has several characteristics in common with aphasia in stroke\textsuperscript{12,54} or tumor patients\textsuperscript{14,15}: activity shifts from the predominantly left-sided lesion site to the right, in particular, in those patients who have comprehension deficit. In the right hemisphere, activity correlates inversely with language performance. The anterior temporal laterality shift provides us with a brain measure for evaluating the effect of behavioral or drug interventions in PPA.

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