

# The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia

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Wernicke's aphasia is characterized by severe word and sentence comprehension impairments. The location of the underlying lesion site, known as Wernicke's area, remains controversial. Questions related to this controversy were addressed in 72 patients with primary progressive aphasia who collectively displayed a wide spectrum of cortical atrophy sites and language impairment patterns. Clinico-anatomical correlations were explored at the individual and group levels. These analyses showed that neuronal loss in temporoparietal areas, traditionally included within Wernicke's area, leave single word comprehension intact and cause inconsistent impairments of sentence comprehension. The most severe sentence comprehension impairments were associated with a heterogeneous set of cortical atrophy sites variably encompassing temporoparietal components of Wernicke's area, Broca's area, and dorsal premotor cortex. Severe comprehension impairments for single words, on the other hand, were invariably associated with peak atrophy sites in the left temporal pole and adjacent anterior temporal cortex, a pattern of atrophy that left sentence comprehension intact. These results show that the neural substrates of word and sentence comprehension are dissociable and that a circumscribed cortical area equally critical for word and sentence comprehension is unlikely to exist anywhere in the cerebral cortex. Reports of combined word and sentence comprehension impairments in Wernicke's aphasia come almost exclusively from patients with cerebrovascular accidents where brain damage extends into subcortical white matter. The syndrome of Wernicke's aphasia is thus likely to reflect damage not only to the cerebral cortex but also to underlying axonal pathways, leading to strategic cortico-cortical disconnections within the language network. The results of this investigation further reinforce the conclusion that the left anterior temporal lobe, a region ignored by classic aphasiology, needs to be inserted into the language network with a critical role in the multisynaptic hierarchy underlying word comprehension and object naming.

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**Abbreviations:** ATL = anterior temporal lobe; PPA = primary progressive aphasia; PPVT = Peabody Picture Vocabulary Test

## Introduction

Nearly 150 years after their introduction into the neurological literature, Broca's area and Wernicke's area continue to attract vigorous research on the functional anatomy of the language network. Over time, 'Broca's area' has become synonymous with the left inferior frontal gyrus (Broca, 1865; Dronkers *et al.*, 2007). This designation is so widely accepted that its location is no longer a subject of scientific debate. Its functionality, however, remains unsettled. Some have argued that damage to Broca's area impairs speech rather than language whereas others have linked it to fundamental disruptions of grammar, lexical retrieval and sentence comprehension (Marie, 1906; Mohr *et al.*, 1978; Benson and Geschwind, 1985; Caplan, 2006; Ochfeld *et al.*, 2009; Thompson *et al.*, 2013). In contrast to the debate on the function of Broca's area, there is broad consensus that Wernicke's area is the region of the brain where lesions cause (or should cause) severe impairments of both word and sentence comprehension (Bogen and Bogen, 1976; Benson and Geschwind, 1985). The challenge posed by Wernicke's area is not what it should be doing but where it might be located (Bogen and Bogen, 1976; DeWitt and Rauschecker, 2013).

The origins of Wernicke's aphasia can be traced to the publication of *Der Aphasische Symptomencomplex* (Wernicke, 1874; Eggert, 1977). Case 2 in that paper (Rother) had a fluent aphasia with impaired comprehension of spoken and written language. Although the brain showed extensive atrophy in both cerebral hemispheres, Wernicke attributed the aphasia to an infarct in the left superior temporal gyrus (Wernicke, 1874). Wernicke did not offer an interpretable anatomical map of this area until the 1881 publication of the *Lehrbuch der Gehirnkrankheiten*, where a shaded region designated the 'sensory speech center' covers the middle two-thirds of the superior temporal gyrus and an adjacent dorsal sliver of the middle temporal gyrus (Wernicke, 1881). For reasons that are not entirely clear, however, the location of this region was pushed back into the posterior third of the superior temporal gyrus by Dejerine (Fig. 1A) and his contemporaries, a relocation that was endorsed by Wernicke in his last major work on aphasia, posthumously published in 1906 (Dejerine and Dejerine-Klumpke, 1895; Bogen and Bogen, 1976; Eggert, 1977).

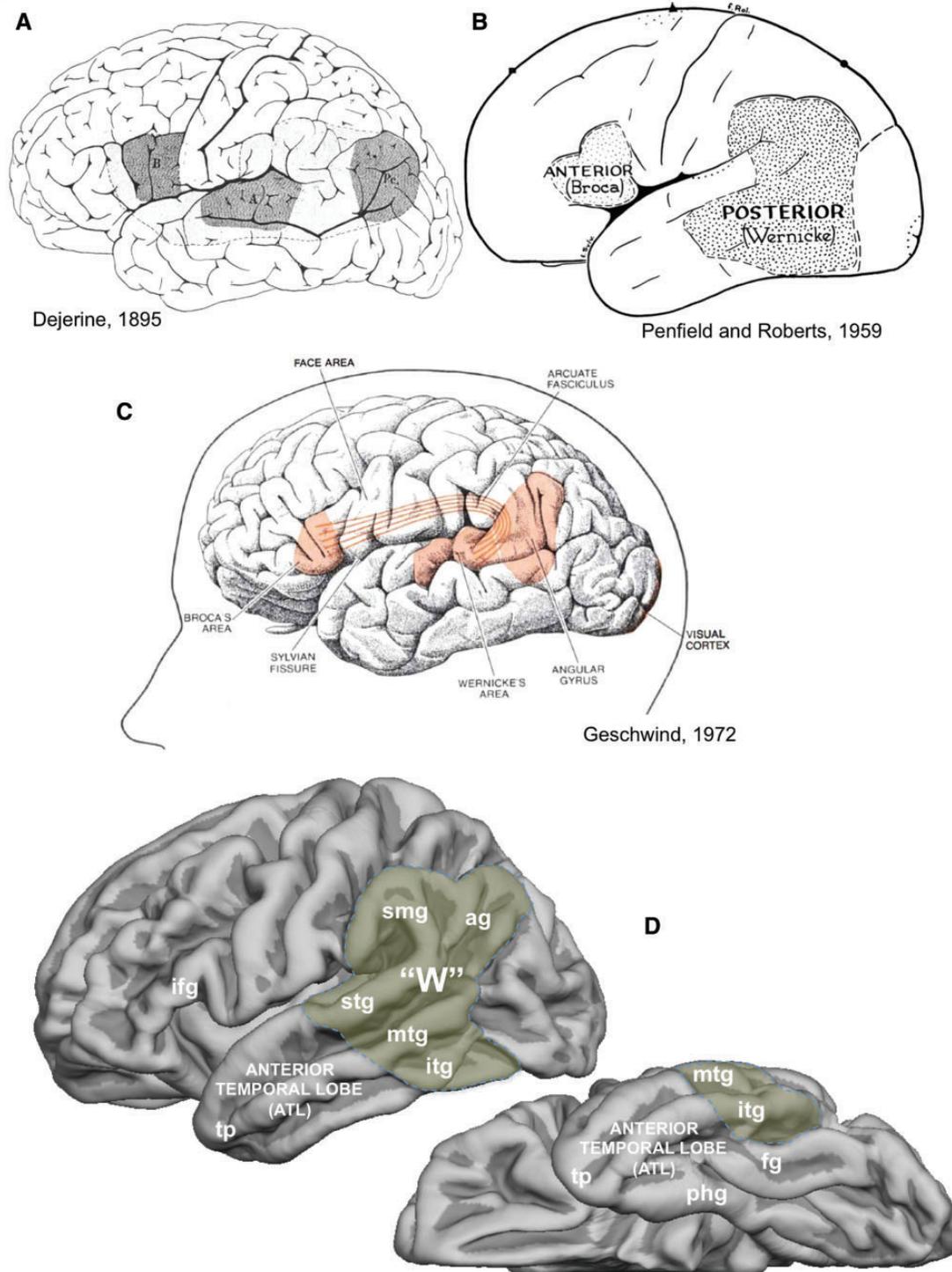
By that time, however, Charcot and Marie had incorporated the adjacent inferior parietal lobule into Wernicke's area, a practice that was adopted by many others (Marie, 1906; Critchley, 1953; Lhermitte and Gautier, 1969; Bogen and Bogen, 1976; Naeser *et al.*, 1987). Still further expansion of Wernicke's area into the middle and inferior temporal gyri appeared in a map of language centres published by Penfield and Roberts (1959; Fig. 1B), based on their experience with excisions of cortical areas (Penfield and Roberts, 1959). This inflationary trend was reversed in the modern literature by several investigators, including

Geschwind and his students (Fig. 1C), who relocated Wernicke's area to the posterior parts of the superior temporal gyrus, but without clear demarcation from the middle temporal and inferior parietal cortices (Geschwind, 1972). A still more recent trend, based on quantitative lesion-symptom mapping studies, is shifting the centre of gravity for the sentence comprehension impairments seen in Wernicke's aphasia to the posterior parts of the middle rather than superior temporal gyrus (Turken and Dronkers, 2011).

Although there is no current consensus on the exact boundaries of Wernicke's area, an aggregate map of locations subsumed under that term would include the supra-marginal and angular gyri of the inferior parietal lobule as well as the posterior parts of the superior, middle and inferior temporal gyri (Fig. 1D). The vast neurological literature that has accumulated since the 1874 publication of *Der Aphasische Symptomencomplex* would then lead to the expectation that the most severe word and sentence comprehension impairments encountered in aphasic patients should be associated with damage within the boundaries of this territory.

This core teaching of clinical neurology, positing an intimate relationship between Wernicke's area and language comprehension, has been challenged by at least two sets of observations. First, electrical stimulation of the anterior fusiform gyrus in the language-dominant hemisphere resulted in severe impairments of word and sentence comprehension, leading the authors to wonder whether this region shared the functionality attributed to Wernicke's area (Lüders *et al.*, 1991). Second, clinico-anatomical correlations in patients with the syndromes of semantic dementia and primary progressive aphasia (PPA) showed that severe word comprehension impairments were associated with atrophy of the anterior rather than posterior temporal lobe (Snowden *et al.*, 1989; Hodges *et al.*, 1992; Rogers *et al.*, 2004; Jefferies and Lambon Ralph, 2006; Patterson *et al.*, 2007; Hurley *et al.*, 2012; Mesulam *et al.*, 2013), a region that was never considered part of Wernicke's area.

How do these two areas, anterior temporal lobe and Wernicke's area, differ in their relationship to word and sentence comprehension? This question has been addressed in patients with Wernicke's aphasia, semantic dementia, and PPA. However, the comparisons in these studies were based on patient groups with different causes of cerebral damage—neurodegenerative for semantic dementia and PPA, and cerebrovascular for Wernicke's aphasia (Jefferies and Lambon Ralph, 2006; Ogar *et al.*, 2011; Robson *et al.*, 2012). Inferences based on lesion-function correlations in these two settings may be subject to fundamental differences (Mesulam *et al.*, 2014). For one, patients with neurodegenerative disease tend to be tested during the progressive phase of a slowly evolving disease whereas patients who have had a stroke are tested at a time when a suddenly acquired lesion is in the phase of recovery and reorganization. To address such potential challenges, the present investigation was initiated to identify atrophy



**Figure 1 Evolution of Wernicke's area.** (A) From Dejerine's textbook (Dejerine and Dejerine-Klumpke, 1895). In this figure 'A' designates Wernicke's centre for auditory images of words, 'B' designates Broca's centre for motor images of articulation, and 'Pc' designates the centre for visual images of words. (B) From Penfield and Roberts (1959). (C) From Geschwind (1972). (D) Lateral and ventral views of the left hemisphere showing a composite rendition of Wernicke's area (W, in green). ag = angular gyrus; fg = fusiform gyrus; ifg = inferior frontal gyrus; itg = inferior temporal gyrus; mtg = middle temporal gyrus; phg = parahippocampal gyrus; smg = supramarginal gyrus; stg = superior temporal gyrus; tp = temporal pole of the ATL.

locations associated with word and sentence comprehension impairments in a set of 72 prospectively enrolled subjects where all patients were assessed with a common set of language tasks and where all lesions were of neurodegenerative origin.

## Materials and methods

The 72 subjects that constituted the reference set for this study (Patients P1–72) were consecutively enrolled in a longitudinal investigation of PPA. The study was approved by the Institutional Review Board of Northwestern University, and informed consent was obtained from all participants. The initial PPA diagnosis was made in the course of a neurological consultation by ascertaining that the patient had a relatively isolated progressive language impairment of neurodegenerative origin (Mesulam, 2001, 2003; Mesulam *et al.*, 2014). Structured interviews and tests of non-language domains were used to confirm that visuospatial processing, explicit memory for recent events, face and object recognition, executive functions and overall comportment were relatively preserved, as required for the root diagnosis of PPA. A second set of tests led to a quantitative evaluation of word comprehension, object naming, sentence comprehension, non-verbal object knowledge, and the ability to repeat phrases and sentences (Mesulam *et al.*, 2012, 2014). An additional inclusion criterion was a Western Aphasia Battery aphasia quotient (Kertesz, 2006) of 60 or higher to exclude patients whose aphasia had progressed beyond the stage at which selective impairments of specific language domains could be identified. All subjects except one were right-handed. The one left-handed subject had greater left hemisphere atrophy, suggesting typical left hemisphere dominance for language. The group contained 33 males and 39 females. According to the 2011 classification guidelines (Gorno-Tempini *et al.*, 2011), the PPA type was agrammatic in 25, semantic in 21, logopenic in 12, and unclassifiable in 14. No further mention of subtypes will be made in this report because the goal was to explore how specific parameters of language function were related to locations of atrophy, regardless of clinical aphasia subtype. Group data on demographics and language parameters are summarized in Table 1.

### Language assessment

Each of the tests used in this investigation was validated in previous studies of PPA (Mesulam *et al.*, 2009, 2012). Word comprehension was tested with a subset of 36 moderately

difficult items (157–192) of the Peabody Picture Vocabulary Test (PPVT-IV; Dunn and Dunn, 2007). Each item requires the patient to match an auditory word representing an object, action or attribute to one of four picture choices. Although the PPVT is a word-picture matching task, less than half of the items represent concrete objects. The majority of the remaining words (e.g. salutation, perplexed, culinary) require extensive associative interpretation (i.e. comprehension) of the words in order to match them to pictorial representations of the corresponding concept. Performance in the PPVT correlates with word–word association tasks (Mesulam *et al.*, 2009). The Boston Naming Test (BNT) was used to assess the naming of objects (Kaplan *et al.*, 1983). It is a 60-item standardized test in which items are administered in order of decreasing frequency of occurrence in the language. Non-verbal object knowledge was assessed with the three picture version of the Pyramids and Palm Trees Test (PPTp; Howard and Patterson, 1992) where the patient is asked to decide which of two pictures is conceptually more closely associated with a target object. The preservation of face recognition, tool handling and object usage in daily activities was further ascertained by systematic questioning of at least one reliable informant. Sentence comprehension was assessed with the most difficult non-canonical items of the Sentence Comprehension Test of the Northwestern Assessment of Verbs and Sentences (NAVS) (Thompson, 2011). In this test, the subject is shown a pair of reversible action pictures and asked to point to the one corresponding to 1 of 15 non-canonical sentences (passive voice, object-extracted ‘Wh’ questions, object relatives). The verbs and nouns used in the test of sentence comprehension (boy, girl, dog, cat, kiss, chase) were of high enough frequency in American English to be understood by all subjects so that poor performance indicated a specific impairment in the comprehension of sentence structure. Repetition of phrases and sentences was tested with the six most difficult items of the Western Aphasia Battery Repetition subtest (Mesulam *et al.*, 2012). To control for differently scaled variables, quantitative performance scores were transformed into a percentage of the total possible score. Control subjects of similar ages and education levels performed all of these tests with accuracy levels of 98% or higher (Mesulam *et al.*, 2012).

### Imaging methods

Structural MRI scans were acquired at Northwestern University’s Centre for Translational Imaging with a 3.0T Siemens scanner and were reconstructed with the FreeSurfer image analysis suite (version 5.1) as previously described (Mesulam *et al.*, 2009; Rogalski *et al.*, 2011). FreeSurfer provides estimates of cortical thickness by measuring the distance

**Table 1** Demographic variables and language scores in Patients P1–72

Age at visit (years)	Education in years	Symptom duration in years	Word Comprehension (PPVT%)	Sentence Comprehension %	Object Naming (BNT%)	Repetition %	Object Association (Pyramids and Palm Trees) %	AQ
64.4 (8) [48–83]	15.8 (3) [8–20]	4.2 (2) [1–11]	77.6 (25) [19–100]	84.4 (17) [46–100]	55.1 (34) [3–98]	75.4 (19) [26–100]	89 (11) [52–100]	82.4 (11) [60–97]

Characteristics of the 72 patients who participated in this study are summarized with means and (standard deviations) and [ranges] of demographic factors and language scores. Performance is expressed as a per cent of the highest possible score. AQ = Aphasia Quotient of the Western Aphasia Battery; BNT = Boston Naming Test.

between representations of the white–grey and pial–CSF boundaries across each point of the cortical surface (Fischl *et al.*, 1999; Fischl and Dale, 2000). Geometric inaccuracies and topological defects were corrected using manual and automatic methods based on validated guidelines (Segonne *et al.*, 2007).

Cortical thickness maps of the PPA patients were statistically contrasted against 35 previously described right-handed age- and education-matched healthy volunteers (Rogalski *et al.*, 2014). Differences in cortical thickness between groups were calculated by conducting a general linear model on every vertex along the cortical surface. False discovery rate (FDR) for individual patient maps was applied at 0.05 to adjust for multiple comparisons and to detect areas of peak cortical thinning (i.e. atrophy) in patients with PPA compared to control subjects (Genovese *et al.*, 2002). A more stringent FDR threshold of 0.0001 was used for detection of significant thinning when patients were considered as a group rather than individually. The relationship between cortical thinning (atrophy) and cognitive performance within the PPA group was assessed using the general linear model with the FDR threshold set at 0.05 (Fischl *et al.*, 1999; Fischl and Dale, 2000).

## Anatomical subdivisions

The anatomical area of interest for this study was the temporal lobe. It was divided into two components. One component, designated ‘W’, represented a composite map of regions where Wernicke’s area has been cited in the literature (Fig. 1). It incorporated the inferior parietal lobule and the posterior half of the temporal lobe. The remaining part was designated ‘anterior temporal lobe’ (ATL) and included the temporal pole at its anterior tip, the anterior parts of the superior, middle and inferior temporal gyri, the parahippocampal gyrus and the anterior fusiform gyrus (Fig. 1D). We realize that ‘W’ and the ATL encompass diverse architectonic areas, each with its own functional attributes. However, our goal was to explore the anatomical correlates of language comprehension as mapped onto the rostrocaudal topography rather than individual subsectors of the temporal lobe, an approach that is consistent with the organization of synaptic processing hierarchies in this part of the brain (Pandya and Seltzer, 1982; Pandya and Yeterian, 1985; Mesulam, 1998).

## General strategy of analyses

To exploit the rich clinicoanatomical information at the individual patient level and also the statistical power of the group as a whole, the data were approached from three vantage points. One was to classify whole-brain cortical thickness maps of individual cases according to the areas that contained peak atrophy and those that were spared at an FDR threshold of 0.05. This approach was used to identify the seven patients with relatively selective ‘W’ atrophy. A second approach was to correlate the magnitude of thinning at each voxel of the whole brain with test scores in the entire patient group to identify the distribution of areas where neuronal loss is most closely associated with impairment of a given function. A third approach was to identify the 10 patients with the lowest scores in word or sentence comprehension tests, irrespective of atrophy distribution, in order to identify lesion sites at the

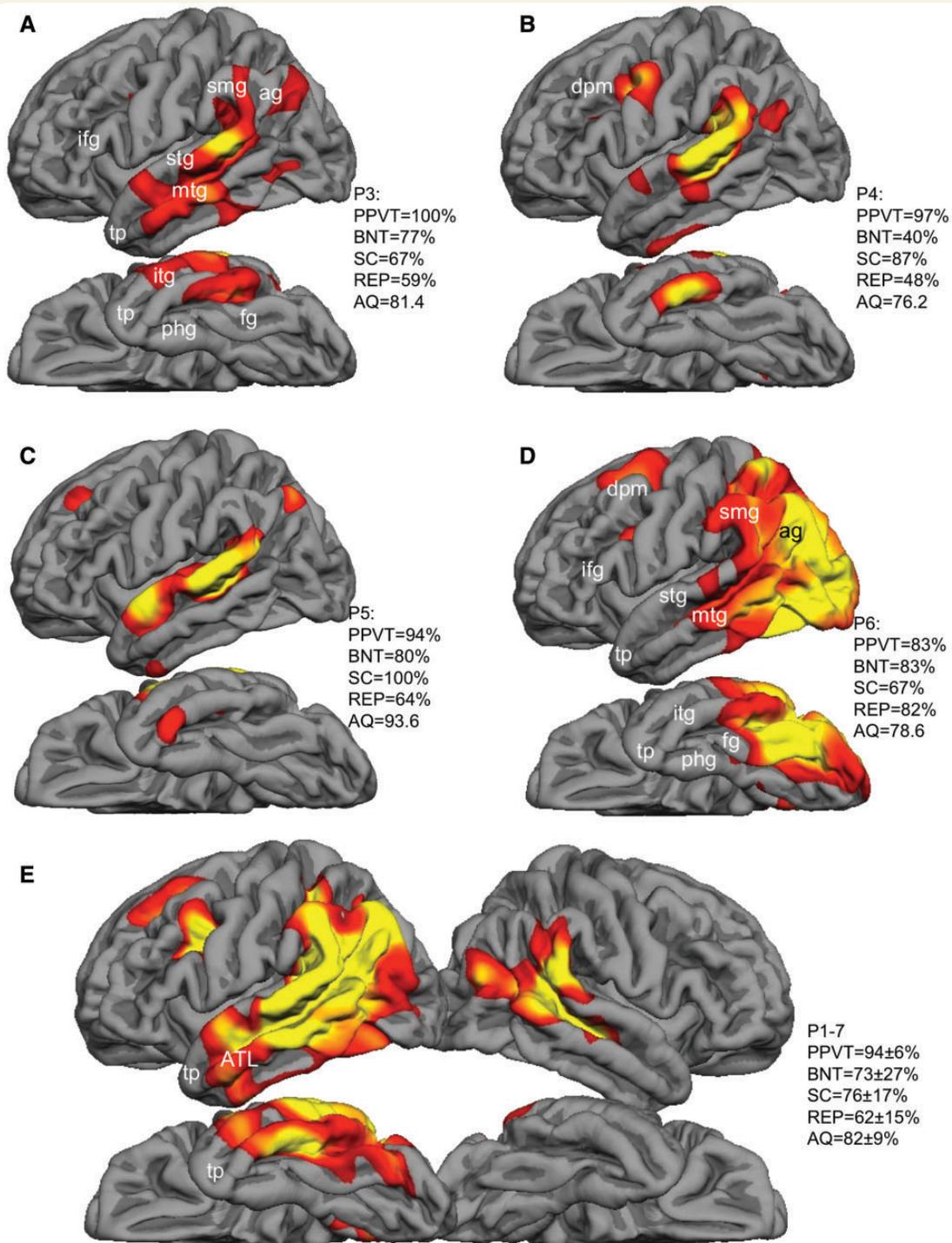
individual patient level that are most important for the integrity of a given functional parameter.

## Results

### Selective ‘W’ atrophy

To determine whether neuronal loss in Wernicke’s area was sufficient to cause the word and sentence comprehension impairments attributed to Wernicke’s aphasia, quantitative FreeSurfer maps comparing each of the 72 patients to the set of 35 controls were analysed to select cases with statistically significant ( $FDR \leq 0.05$ ) peak atrophy sites within the ‘W’ region delineated in Fig. 1D. The selection criteria were purely anatomical, without consideration of language performance patterns. Patients with additional peak atrophy sites that encompassed the anterior tip of the ATL or the inferior frontal gyrus of the left hemisphere were excluded, as damage to these areas are known to impair comprehension of words and sentences, respectively (Ochfeld *et al.*, 2009; Mesulam *et al.*, 2013). Seven participants fit these criteria (Patients P1–7). Twelve other participants had atrophy within the ‘W’ territory but were not included in this group because of additional peak atrophy sites in the inferior frontal gyrus or anterior tip of the ATL. Atrophy maps and test scores of four examples and of the group as a whole are shown in Fig. 2. The atrophy displayed prominent leftward asymmetry and, in the group as a whole, covered all the territory traditionally included within Wernicke’s area. In some patients, it also extended into the posterior parts of the ATL, dorsal premotor cortex, and anterior occipital lobe (Fig. 2).

Word comprehension performance in Patients P1–7 was excellent, with mean PPVT accuracy of  $94 \pm 6\%$  (Fig. 2E). Object naming performance assessed by the Boston Naming Test was variable and ranged from very impaired (30–40% in two of the patients) to nearly perfect (98% in two of the patients), without consistent differences of peak atrophy sites that could explain the variability (Fig. 2B versus C). Sentence comprehension displayed mean accuracy of  $76 \pm 17\%$ . Performance on this task was excellent in two of the patients (87% and 100% correct) and severely impaired (53%) in only one. Repetition scores were in the distinctly impaired range in five of seven patients, with a performance range of 41–61%, a finding that confirms the role of the temporoparietal junction and adjacent parts of the superior temporal gyrus in phonological processing (Gorno-Tempini *et al.*, 2008; Rogalski *et al.*, 2011). Although sentence comprehension scores were significantly correlated with repetition scores, the correlation coefficient was low and accounted for <20% of the variance (Table 2). In fact, dissociations between sentence comprehension and repetition impairments were common at the individual patient level (Fig. 2C versus D). The group was too small for meaningful quantitative correlations among



**Figure 2 Atrophy maps in Wernicke's area in Patients P1-7.** (A-D) Individual atrophy maps of the left hemisphere and performance in language tasks for four patients with atrophy sites that illustrate the anatomical variability but also the common features of peak atrophy sites within the 'W' territory of Fig. 1D but without involving the inferior frontal gyrus or tip of the anterior temporal lobe. (E) Atrophy map in both hemispheres for the whole group. ag = angular gyrus; AQ = Aphasia Quotient of the Western Aphasia Battery; BNT = Boston Naming Test; dpm = dorsal premotor cortex; fg = fusiform gyrus; ifg = inferior frontal gyrus; itg = inferior temporal gyrus; mtg = middle temporal gyrus; phg = parahippocampal gyrus; REP = repetition test; SC = sentence comprehension test; smg = supramarginal gyrus; stg = superior temporal gyrus; tp = temporal pole of the ATL.

**Table 2** Intercorrelations of language scores in Patients P1–72

	Object naming	Sentence comprehension	Repetition	Non-verbal object recognition
Word Comprehension	0.776* ( $< 0.001$ ) [n = 69]	−0.117 (0.367) [n = 62]	−0.088 (0.477) [n = 68]	0.749* ( $< 0.001$ ) [n = 67]
Object naming		−0.033 (0.796) [n = 63]	0.142 (0.236) [n = 71]	0.611* ( $< 0.001$ ) [n = 69]
Sentence comprehension			0.406* ( $< 0.001$ ) [n = 62]	0.050 (0.698) [n = 63]
Repetition				−0.043 (0.725) [n = 68]

Two-tailed Pearson correlations and (significance) in the set of 72 patients. Not all patients completed all the tests. The *n* values indicate the number of patients included in each correlation.

test results or between test scores and distribution of cortical thinning.

### Correlations of atrophy with comprehension scores in the set of 72 patients

Results in Patients P1–7 showed that neuronal loss in ‘W’ leaves word comprehension intact and that it displays no consistent relationship to sentence comprehension. To identify the location of atrophy sites most closely associated with sentence and word comprehension, performance scores in the entire patient set were correlated with regional variations of cortical thickness (Fig. 3). Sixty-three subjects had sentence comprehension scores and 67 had word comprehension scores. Considering the high correlation coefficient of word comprehension with non-verbal object identification (Table 2), accounting for ~50% of the variance, the correlation map for word comprehension was generated with the Pyramids and Palm Trees Test as a variable of nuisance. The overall analysis showed that sentence and word comprehension were correlated with cortical thickness in two completely different sets of areas. Sentence comprehension (i.e. the ability to decode grammatical structure in sentences where the constituent words could be understood easily) was associated with atrophy predominantly in the left supramarginal and angular gyri (posterior parts of ‘W’), inferior frontal gyrus (IFG, Broca’s area), dorsal frontal cortex and anterior orbitofrontal cortex (Fig. 3A). Word comprehension impairments, on the other hand, were correlated with atrophy predominantly in the left ATL including its polar component (Fig. 3B). When the contribution of Pyramids and Palm Trees Test was ignored, atrophy areas correlated with word comprehension deficits extended slightly more posteriorly within the middle and inferior temporal gyri but still failed to display any overlap with atrophy areas

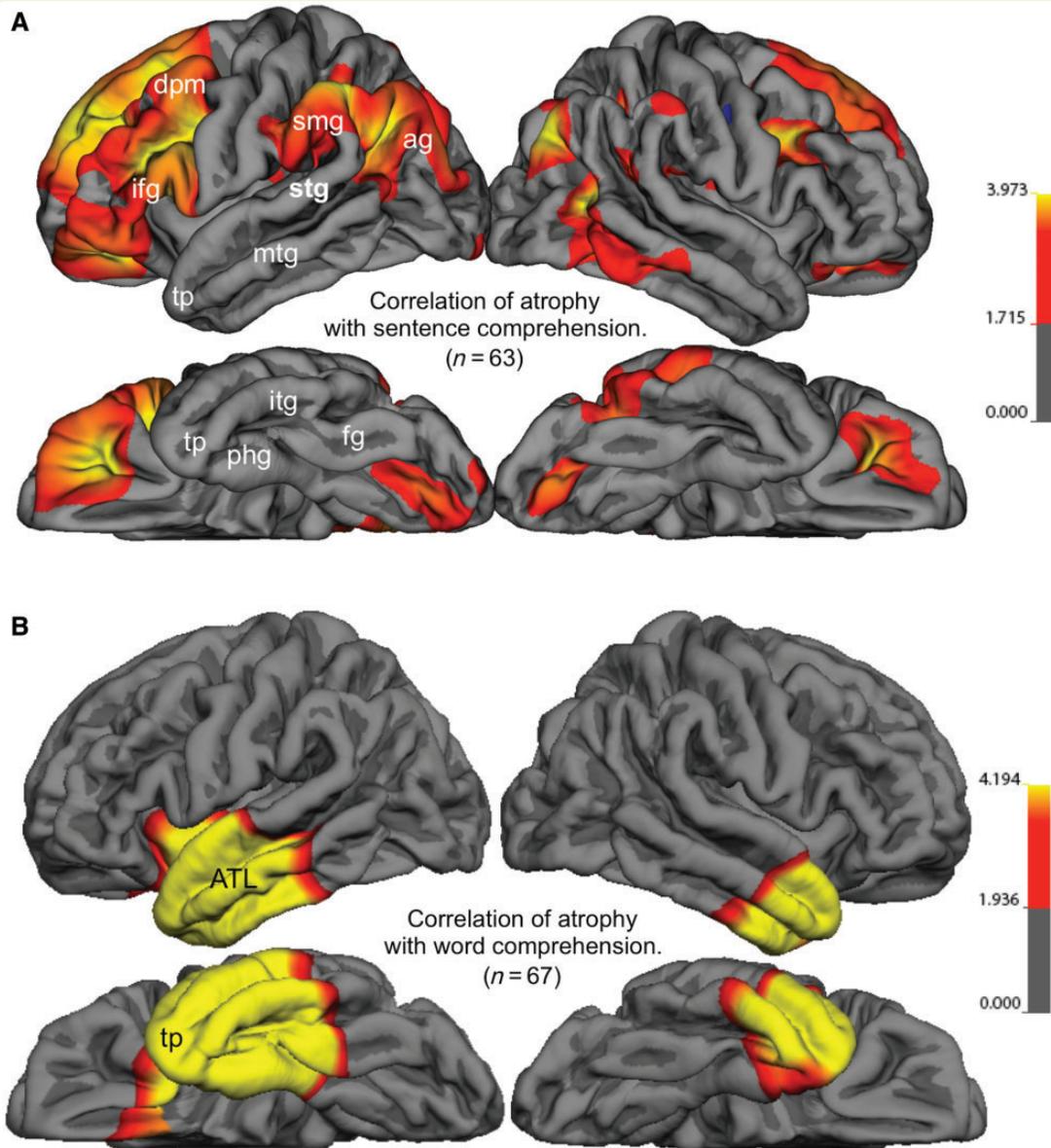
correlated with sentence comprehension impairment (see Supplementary material). In keeping with this anatomical dissociation, there was no significant correlation of sentence comprehension scores with scores of word comprehension in the entire set of PPA patients who had been given the relevant tests (Table 2).

### Atrophy in individual patients with the most severe sentence comprehension impairments

The correlation map in Fig. 3A, showing that neuronal loss in posterior parts of ‘W’ is correlated with sentence comprehension impairments, may initially appear to be at odds with the results in Patients P1–7, which revealed no consistent relationship between ‘W’ atrophy and such impairments. However, Fig. 3A does not specify the putative boundaries of atrophy sites that are either sufficient or necessary to cause severe sentence comprehension impairments. To address this question, the performance scores of all patients were reviewed to identify the 10 patients (Patients P6–15) with the lowest sentence comprehension scores irrespective of atrophy distribution (Table 3). The individual distribution of peak atrophy in these patients was determined by quantitative FreeSurfer maps that delineated areas of significant thinning in comparison to the 35 controls. Only two of the patients (Patients P6 and P7) with selective ‘W’ atrophy fit into this group (e.g. Patient P6 in Fig. 2). Three others also had prominent atrophy in parts of ‘W’ but with additional peak atrophy sites in the left inferior frontal gyrus, dorsal premotor cortex, or parts of ATL. In the remaining five, atrophy spared ‘W’ but variably involved inferior frontal gyrus, dorsal premotor cortex or ATL. In summary, half of the 10 patients with the most severe sentence comprehension impairments had no significant atrophy in ‘W’ even with the lenient FDR threshold of 0.05. The posterior parts of ‘W’ may therefore influence sentence comprehension but without playing a uniquely critical role in maintaining the integrity of this function. These results show that the distribution of peak atrophy associated with severe sentence comprehension impairment is highly variable at the level of individual patients, but with a group distribution that remains mostly confined within the boundaries of the correlation map in Fig. 3A.

### Atrophy sites in individual patients with the most severe word comprehension impairments

A similar analysis was carried out in the group of 10 patients (Patients P16–25) with the most severe word comprehension impairments (mean of  $31.2 \pm 7.5\%$ , range 19–42%) (Table 3). In distinct contrast to the anatomical variability of peak atrophy sites in Patients P6–15, the 10 patients with the lowest word comprehension scores had remarkably consistent peak atrophy sites that closely



**Figure 3** Correlations of cortical thinning (atrophy) with language comprehension scores. FDR threshold was set at 0.05. The heat map numbers indicate  $-\log_{10}$   $P$ -values of significance. **(A)** Sites where atrophy correlates with sentence comprehension impairment. **(B)** Sites where atrophy correlates with word comprehension impairment when non-verbal object recognition scores are considered nuisance variables. ag = angular gyrus; dpm = dorsal premotor cortex; fg = fusiform gyrus; ifg = inferior frontal gyrus; itg = inferior temporal gyrus; mtg = middle temporal gyrus; phg = parahippocampal gyrus; smg = supramarginal gyrus; stg = superior temporal gyrus; tp = temporal pole of the ATL.

**Table 3** Performance patterns in three patient groups

	PPVT%	BNT%	SC%	Repetition%	PPTp%	AQ
Patients P6–15: 10 lowest SC scores	81.9 (17.4)	62.2 (33.6)	56.5 (6.8)	68.6 (17.4)	88.2 (15)	77.4 (6.5)
Patients P16–25: 10 lowest PPVT scores	31.2 (7.5)	8.2 (3.4)	92.5 (9)	75.5 (11.9)	72.4 (10.9)	75 (6.6)
Patients P26–33: ATL + TP atrophy with spared PPVT	93 (6.4)	57.5 (27.7)	88.6 (16.1)	90.6 (9.1)	95.7 (3.1)	85.6 (6.7)

Performance on language tasks with means and (standard deviations) are shown in three patient groups. Patients P6–15 are the patients with the 10 lowest sentence comprehension (SC) scores; Patients P16–25 are the patients with the 10 lowest word comprehension (PPVT) scores; and Patients P26–33 are the only eight patients with left ATL atrophy that included the temporal pole (TP) but without impairing word comprehension. Performance is expressed as a per cent of the highest possible score. AQ = Aphasia Quotient of the Western Aphasia Battery; BNT = Boston Naming Test; PPTp = picture form of the Pyramids and Palm Trees Test; SC = sentence comprehension test.

matched the correlation map of Fig. 3B. In all 10 patients, peak atrophy was asymmetrical and invariably covered the left temporal pole and adjacent ATL (see Fig. 4A–C for three examples). In half of the cases, peak atrophy extended into the anterior parts of the ‘W’ territory but in the form of an extension from the ATL focus. The parahippocampal and anterior fusiform gyri were included within the region of peak atrophy in the majority but not all of the cases. The mean non-verbal object recognition scores were highly variable (mean  $72.4 \pm 10.9\%$ ) but distinctly better than the word comprehension scores (Table 3). Two of four cases with the lowest non-verbal object recognition scores were also the only ones with additional atrophy at the tip of the contralateral right temporal lobe and displayed features that overlapped with those of semantic dementia. In 8 of 10 patients, significant atrophy was unilateral and confined to the ATL of the left hemisphere. In addition to word comprehension impairments, Patients P16–25 consistently displayed severe object naming abnormalities (mean of  $8.2 \pm 3.4\%$  and range of 5–13%). Sentence comprehension was nearly intact in all members of this group (mean of  $92 \pm 9\%$ ).

### Status of the temporal pole in word comprehension

In the P1–7 group, peak atrophy extended into a rim of ATL adjacent to the ‘W’ territory but not into the temporal pole (Fig. 2E). This atrophy pattern left single word comprehension relatively intact. In contrast, the ATL peak atrophy sites associated with severe word comprehension impairment consistently included the temporal pole (Fig. 4). There were 37 patients in the set of 72 where peak atrophy spared the left temporopolar region and all of these patients had word comprehension scores  $\geq 80\%$ , a cut-off we previously used to indicate relative sparing of function (Mesulam *et al.*, 2012). It appears, then, that ATL neuronal loss causes major word comprehension impairments only if it extends anteriorly all the way into the polar region.

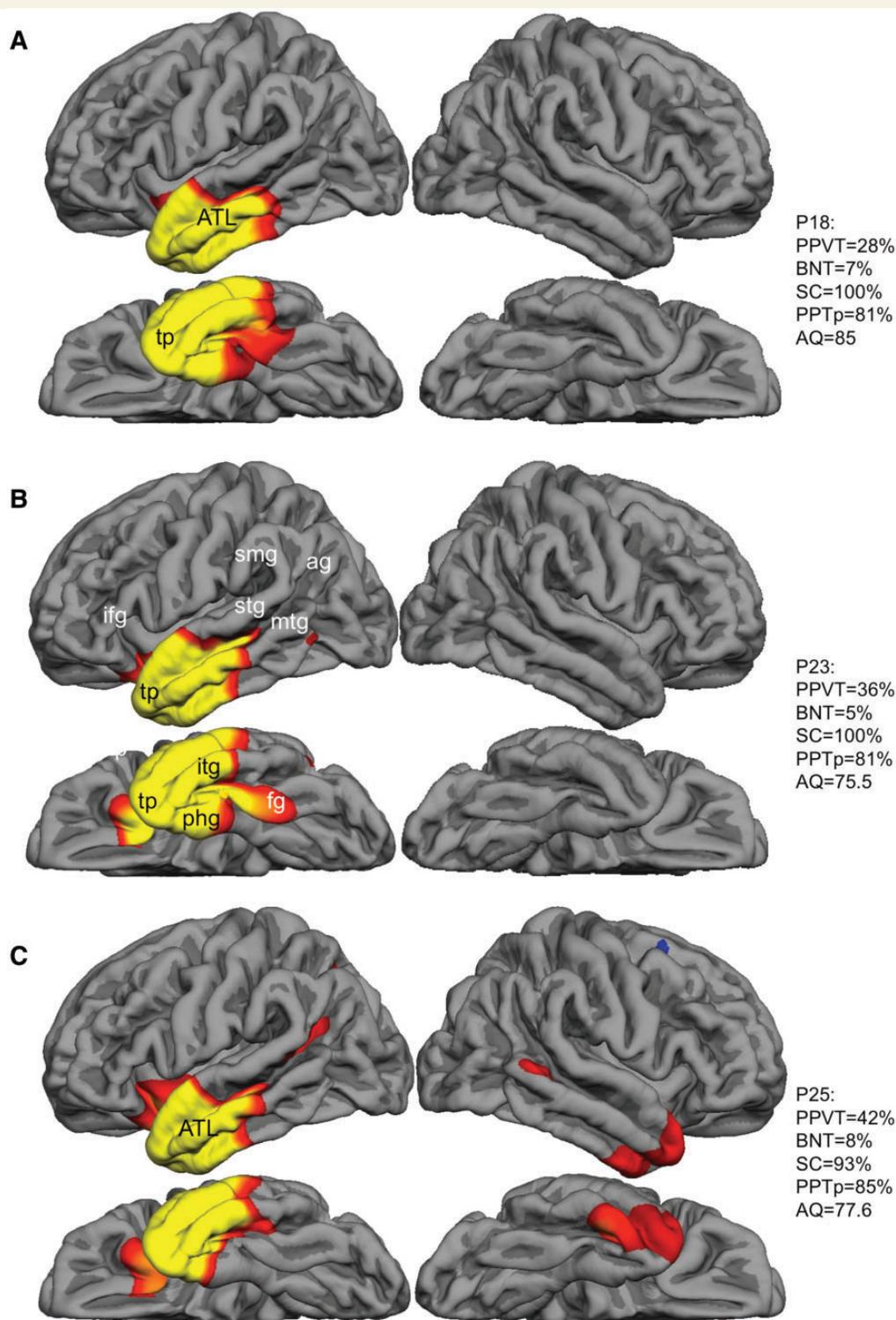
There were no cases of ATL atrophy entirely confined to the pole. ATL atrophy that included the polar region was seen in 35 of 72 patients. Eight of these (23%) maintained word comprehension scores  $\geq 80\%$  (Patients P26–33). Object naming was the only area of severe impairment in these patients (Table 3). One of the patients in this group (Patient P26) initially had atrophy restricted to the temporal pole and a narrow rim of immediately adjacent ATL. He was retested 4 years later and displayed severe word comprehension impairment at a time when the atrophy had spread to the remaining parts of the ATL (Fig. 5). The observations based on Patients P26–33 provide circumstantial evidence that an isolated anomia represents a prodromal stage of the word comprehension impairment caused by neuronal loss in the ATL.

## Discussion

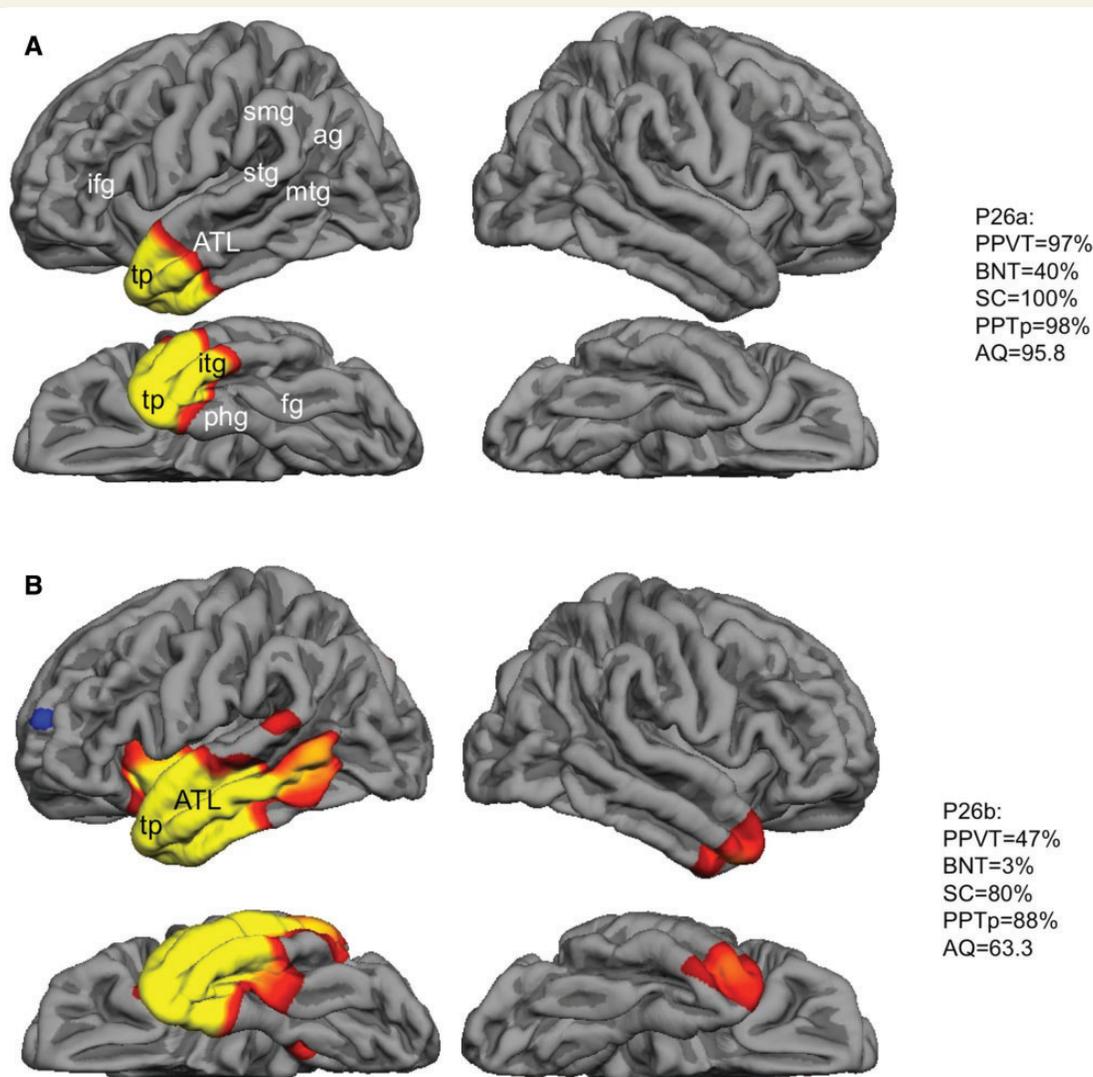
This study showed that neuronal loss within the traditional boundaries of Wernicke’s area is not associated with the language comprehension impairment classically attributed to Wernicke’s aphasia and that word and sentence comprehension abilities have non-overlapping anatomical substrates. The methodology in this study had strengths and weaknesses. A major advantage was the analysis of clinico-anatomical comparisons within and across patient groups where all members had a neurodegenerative disease affecting predominantly the cerebral cortex. Given the neuropathological heterogeneity of PPA, however, the 72 patients in this study are likely to have had different causes of neurodegeneration (Mesulam *et al.*, 2014). Although unlikely, it is therefore prudent to consider the possibility that different neuropathological entities may differentially impact the function of atrophy sites, perhaps through differential destruction of cellular components. A more important consideration is the fact that the morphometric method used in this study reveals only areas of statistically significant thinning and may therefore overlook subthreshold thinning that may exist elsewhere in the cerebral cortex. Conversely, neuronal destruction within sites of maximal atrophy is never complete, and residual neurons are likely to maintain some functionality, albeit with distorted connectivity patterns (Sonty *et al.*, 2003, 2007; Vandenbulcke *et al.*, 2005; Mesulam *et al.*, 2014). Although these potential caveats caution against simple clinico-anatomical inferences, they should have had an equal impact upon all subjects in this study without necessarily undermining the validity of the dissociations that were demonstrated in the anatomical substrates of word versus sentence comprehension.

### Wernicke’s area and altered comprehension of sentences but not words

Peak atrophy sites covering the territory assigned to Wernicke’s area failed to impair single word comprehension. This finding is inconsistent with the prominent word comprehension impairments reported in patients with Wernicke’s aphasia and attributed to lesions in Wernicke’s area (Kertesz, 1983; Naeser *et al.*, 1987; Damasio and Damasio, 1989; Hillis *et al.*, 2001; DeLeon *et al.*, 2007; Ogar *et al.*, 2011; Robson *et al.*, 2012). The objection could be raised that this negative result reflects the activity of residual neurons in Wernicke’s area. However, it is difficult to see why the impact of residual neurons should have been greater in Wernicke’s area than in the anterior temporal lobe where atrophy caused severe impairments of word comprehension. This sparing of single word comprehension in lesions of Wernicke’s area has also been demonstrated in a recent quantitative study of cerebrovascular lesions using multivariate voxel-based



**Figure 4 Word comprehension and anterior temporal lobe atrophy.** (A–C) Individual atrophy maps and language performance scores in three members of Group P16–25 (the subjects with the 10 lowest word comprehension scores). The three examples display the consistency of the atrophy patterns seen in the group as a whole. ag = angular gyrus; AQ = Aphasia Quotient of the Western Aphasia Battery; BNT = Boston Naming Test; fg = fusiform gyrus; ifg = inferior frontal gyrus; itg = inferior temporal gyrus; mtg = middle temporal gyrus; phg = parahippocampal gyrus; PPTp = picture form of the Pyramids and Palm Trees Test; SC = sentence comprehension test; smg = supramarginal gyrus; stg = superior temporal gyrus; tp = temporal pole of the ATL.



**Figure 5** Progression of atrophy in the anterior temporal lobe. (A) Patient P26 has temporopolar atrophy but nearly intact single word comprehension. Severe naming impairment (BNT performance of 40%) stands out as the principal finding. (B) Four years later the atrophy extends further into the anterior temporal lobe and is associated with severe single word comprehension impairment. ag = angular gyrus; AQ = Aphasia Quotient of the Western Aphasia Battery; BNT = Boston Naming Test; fg = fusiform gyrus; ifg = inferior frontal gyrus; itg = inferior temporal gyrus; mtg = middle temporal gyrus; phg = parahippocampal gyrus; PPTp = picture form of the Pyramids and Palm Trees Test; SC = sentence comprehension test; smg = supramarginal gyrus; stg = superior temporal gyrus; tp = temporal pole of the ATL.

lesion–symptom mapping in 40 chronic ischaemic stroke patients (Pillay *et al.*, 2014).

The relationship of Wernicke’s area to sentence comprehension was complex. Group analyses showed that Wernicke’s area is one of several regions, including Broca’s area and dorsal frontal cortex, where atrophy is significantly correlated with sentence comprehension impairment. In individual cases, however, half of the 10 patients with the most severely impaired sentence comprehension abilities had no significant atrophy in Wernicke’s area whereas some others had intact sentence comprehension despite considerable atrophy in this region. The sentence comprehension test we used was particularly challenging and engaged auditory working memory as well as the ability to decode relatively

complex grammatical structure. The underlying mechanisms of poor performance could therefore vary from patient to patient. In some patients with ‘W’ atrophy the impairment could have been mediated by a perturbation of phonological processing, a function that has been linked to parts of ‘W’ by investigations in PPA and cerebrovascular accidents (Gorno-Tempini *et al.*, 2008; Rogalski *et al.*, 2011; Robson *et al.*, 2013; Pillay *et al.*, 2014). The association of the most severe impairments with peak atrophy sites not only in Wernicke’s area, but also in Broca’s area and dorsal premotor cortex is consistent with an extensive literature on the anatomy of sentence comprehension impairments in stroke and PPA (Grodzinsky and Friederici, 2006; Amici *et al.*, 2007; Wilson *et al.*, 2010; Ogar *et al.*, 2011; Turken

and Dronkers, 2011; Tyler *et al.*, 2011; Newhart *et al.*, 2012; Mack *et al.*, 2013; Thompson and Kiehl, 2014).

## Anterior temporal lobe and word comprehension

The test scores in the 72 patients revealed no significant correlation between word and sentence comprehension impairment. In keeping with this finding, peak atrophy sites associated with word comprehension failures displayed a complete dissociation from those associated with sentence comprehension impairment. Group and individual patient analyses consistently showed a correlation of word comprehension impairment with atrophy of the temporal pole and adjacent ATL of the left hemisphere. These results confirm prior quantitative morphometric investigations of PPA where PPVT performance was correlated with cortical thinning confined to the anterior temporal lobe (Rogalski *et al.*, 2011). As previously reported in PPA (Ogar *et al.*, 2011), atrophy in the ATL left sentence comprehension mostly intact in this set of patients. However, an investigation based on cerebrovascular lesions and another based on functional imaging in normal subjects, had reported ATL contributions to sentence comprehension (Humphries *et al.*, 2006; Magnusdottir *et al.*, 2012). These results need to be interpreted with caution since functional imaging cannot distinguish collateral from critical components of a network and since cerebrovascular lesions are subject to anatomical uncertainties arising from the destruction of underlying fibre tracts. It is quite remarkable that the spared parts of the brain in Patients P16–25 (Fig. 4), namely all cortical areas outside the left ATL, were incapable of sustaining the ability to understand even relatively common words or name familiar objects. It appears that the neuronal substrates critical for word comprehension are much more concentrated than those critical for sentence comprehension.

## Wernicke's aphasia as a double disconnection syndrome

The results of this study are in conflict with the classic neurological literature, which associates damage to Wernicke's area with severe impairments of both sentence and word comprehension. One resolution of this discrepancy lies in the nature of patient populations that have been investigated. The literature on Wernicke's aphasia is almost exclusively based on patients with cerebrovascular lesions (Wernicke, 1874; Kertesz, 1983; Naeser *et al.*, 1987; Damasio, 1989; Jefferies and Lambon Ralph, 2006; Ogar *et al.*, 2011). In publications where lesion sites have been illustrated, the damage has invariably extended deep into underlying white matter. This is not surprising since the angular, posterior temporal and posterior parietal branches of the left middle cerebral artery, occlusions of which can be associated with Wernicke's aphasia, supply Wernicke's area as well as the underlying white matter

(Damasio, 1983). A stroke within one of these vascular territories can not only destroy the cortex within Wernicke's area and interfere with its phonological functions, but also cause white matter destruction that disconnects residual and healthy parietotemporal cortices from other components of the language network. The dorsal axis of this disconnection, affecting communications with Broca's area and adjacent frontal cortices, may impair sentence comprehension whereas the ventral component, affecting communications with the anterior temporal lobe, may impair word comprehension, jointly leading to the syndrome of Wernicke's aphasia. Wernicke's aphasia can thus be considered a double disconnection syndrome or a 'hodological' syndrome in Catani's nomenclature (Catani and Mesulam, 2008).

## Wernicke's area and the multisynaptic matrix underlying word comprehension

The region designated 'W' in Fig. 1D includes the primary and associative auditory cortices of the superior temporal gyrus (Mesulam, 2000). Neurons in these areas are known to participate in word comprehension at least in part by their known ability to encode the word-like properties and intelligibility of auditory input (Creutzfeldt *et al.*, 1989; Mesulam, 1998; Scott *et al.*, 2000; Wise *et al.*, 2001; DeWitt and Rauschecker, 2013). It is reasonable to assume that auditory inputs that are both word-like and intelligible will be the most likely to gain preferential entry into anteriorly directed multisynaptic hierarchies of the language-dominant temporal lobe. In the course of the synaptic elaboration within this feed-forward hierarchy, words are expected to evoke the distributed associations that collectively define their meaning. In the case of a concrete noun, this will include associative interactions with the inferotemporal object recognition network (Mesulam, 1998). Another pivotal component is the generation of reciprocal top-down (feedback) signals by anterior (downstream) parts of the synaptic chain so that the interpretation of the anteriorly propagated associations becomes guided by prior knowledge and current expectations (Damasio, 1989; Grabowski *et al.*, 2001; Friston, 2005; Mesulam, 2008). The computational importance of top-down guidance emanating from the more anterior components of the underlying synaptic chain may explain why neuronal loss at the anterior temporal lobe, including its polar component, plays such a critical role in word comprehension (Schwartz *et al.*, 2009; Mesulam *et al.*, 2013).

According to this organization of neural events, atrophy confined to Wernicke's area might not be sufficient to cause severe multimodal word comprehension impairment, probably because residual temporoparietal neurons of the left hemisphere and transcallosal inputs from the contralateral side can continue to supply the left anterior temporal lobe with sufficient word-form input. This hypothesis is

also consistent with studies showing that remaining verbal comprehension abilities in patients with Wernicke's aphasia is sustained by anterior temporal lobe activity (Crinion *et al.*, 2006; Robson *et al.*, 2014).

The associative linkage of a noun to the object it denotes can be perturbed by disruptions anywhere along the synaptic web described above. This is why anomia is one of the most frequent manifestations of damage to the left temporal lobe (DeLeon *et al.*, 2007; Rohrer *et al.*, 2008), and why it was detected in all patient groups of this study. The fact that the most severe anomic deficits were generally encountered in patients who also had severe comprehension impairment underscores the interdependence of word comprehension and object naming. When atrophy of the anterior temporal lobe remains below a certain threshold, as in the case of the patient illustrated in Fig. 5, severe anomia can arise even without word comprehension impairment. In fact, cortical stimulation of the anterior fusiform gyrus showed that low intensities led to anomia whereas high intensities also triggered severe comprehension impairments (Lüders *et al.*, 1991).

## Conclusion

The fundamental dissociation between single word comprehension and sentence comprehension demonstrated by this study reflects the profoundly different computational processes that underlie these two aspects of language function. Although impairments of both word and sentence comprehension do arise in the syndromes of word deafness and word blindness, the deficits in these syndromes are unimodal and reflect the sensory deafferentation rather than the selective destruction of language cortices. It is therefore reasonable to conclude that a circumscribed multimodal region, where cortical neurons are equally critical for word and also sentence comprehension, does not exist in any of the regions assigned to Wernicke's area, or anywhere else in the cerebral cortex.

As the maps in Fig. 1 show, the left anterior temporal lobe had not been included within the classic language network. The possibility of such an affiliation was explicitly considered and rejected in a pivotal review by Bogen and Bogen (1976). In that review, the authors wondered whether it would be possible to have a probabilistic approach to aphasia-causing lesion sites, especially those related to comprehension. 'And the answer' they wrote 'is that it [the probability] is very high in or near the first temporal gyrus, and fades out with different gradients (varying among individuals) toward the poles. And by the time it gets to any pole (occipital, temporal, or frontal) the probability is essentially zero.' (Bogen and Bogen, 1976).

Although studies on herpes simplex, temporal lobectomy, intraoperative cortical stimulation, functional imaging, and voxel-based lesion-symptom matching had revealed language-related functions of the ATL (Heilman, 1972; Ojemann, 1983; Warrington and Shallice, 1984;

Damasio, 1992; Gitelman *et al.*, 2005; Schwartz *et al.*, 2011), it took investigations on semantic dementia and PPA to reveal the profound importance of this region to language function (Snowden *et al.*, 1989; Hodges *et al.*, 1992; Rogers *et al.*, 2004; Jefferies and Lambon Ralph, 2006; Patterson *et al.*, 2007; Hurley *et al.*, 2012; Mesulam *et al.*, 2013). The results of the current study reinforce this growing body of evidence and support the conclusion that the left anterior temporal lobe needs to be inserted into the canonical language network with a critical role in single word comprehension and object naming, a relationship that seems to have eluded classic aphasiology, probably because this region rarely becomes the site of isolated cerebrovascular lesions.

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## Supplementary material

Supplementary material is available at *Brain* online.

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