Word comprehension in temporal cortex and Wernicke area

A PPA perspective

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Abstract

Objective

To explore atrophy–deficit correlations of word comprehension and repetition in temporoparietal cortices encompassing the Wernicke area, based on patients with primary progressive aphasia (PPA).

Methods

Cortical thickness in regions within and outside the classical Wernicke area, measured by FreeSurfer, was correlated with repetition and single word comprehension scores in 73 right-handed patients at mild to moderate stages of PPA.

Results

Atrophy in the Wernicke area was correlated with repetition ($r = 0.42$, $p = 0.001$) but not single word comprehension ($r = -0.072$, $p = 0.553$). Correlations with word comprehension were confined to more anterior parts of the temporal lobe, especially its anterior third ($r = 0.60$, $p < 0.001$). A single case with postmortem autopsy illustrated preservation of word comprehension but not repetition 6 months prior to death despite nearly 50% loss of cortical volume and severe neurofibrillary degeneration in core components of the Wernicke area.

Conclusions

Temporoparietal cortices containing the Wernicke area are critical for language repetition. Contrary to the formulations of classic aphasiology, their role in word and sentence comprehension is ancillary rather than critical. Thus, the Wernicke area is not sufficient to sustain word comprehension if the anterior temporal lobe is damaged. Traditional models of the role of the Wernicke area in comprehension are based almost entirely on patients with cerebrovascular lesions. Such lesions also cause deep white matter destruction and acute network diaschisis, whereas progressive neurodegenerative diseases associated with PPA do not. Conceptualizations of the Wernicke area that appear to conflict, therefore, can be reconciled by considering the hodologic and physiologic differences of the underlying lesions.

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Glossary

AG = angular gyrus; **AT** = anterior temporal; **BNT** = Boston Naming Test; **FDR** = false discovery rate; **GRAM** = grammatically correct sentences; **IFG** = inferior frontal gyrus; **IFG-B** = inferior frontal gyrus combined into a single sector containing the Broca area; **IPL** = inferior parietal lobule; **ITG** = inferior temporal gyrus; **MT** = middle temporal; **MTG** = middle temporal gyrus; **NFT** = neurofibrillary tangle; **pMTG** = posterior middle temporal gyrus; **PPA** = primary progressive aphasia; **PPVT-IV** = Peabody Picture Vocabulary Test; **pSTG** = posterior superior temporal gyrus; **PT-W** = parietotemporal sector encompassing the Wernicke area; **ROI** = region of interest; **SG** = supramarginal gyrus; **STG** = superior temporal gyrus; **WAB-R-AQ** = Western Aphasia Battery–Revised Aphasia Quotient.

The term Wernicke area has traditionally designated posterior components of the language network where lesions impair comprehension. A perennial debate addresses the question of whether the Wernicke area should be assigned a fixed location or whether it should be defined by the position of lesions that impair comprehension.¹ Wernicke² located the lesion of his paradigmatic patient Rother within the midposterior left superior temporal gyrus (STG). During the ensuing century, the inferior parietal lobule (IPL) and posterior middle temporal gyrus (pMTG) were variably incorporated into the Wernicke area based on the anatomy of lesions impairing comprehension.^{1,3} More contemporary reports confine the Wernicke area mostly to posterior STG (pSTG).^{4–6} However, while some investigators conclude that pSTG is essential for comprehension,⁷ others disagree.^{5,6,8–10} The roles of IPL and pMTG in comprehension are topics of intensive investigation.^{3,6,11,12}

Classical accounts linking the Wernicke area to comprehension relied on stroke patients.^{7,13} However, investigations on primary progressive aphasia (PPA) and semantic dementia have associated comprehension impairments with atrophy in anterior temporal (AT) cortex rather than the Wernicke area.^{3,14–16}

As these conclusions based on neurodegenerative diseases conflicted with classic aphasiology,³ they have been criticized.^{7,17} This report addresses these objections through quantitative correlations of comprehension and other language functions with cortical atrophy throughout temporal neocortex, including the Wernicke area. New analyses on a previously reported cohort³ of 73 patients with PPA are supplemented by neuropathologic data from a patient who died 6 months after testing and imaging.

Methods

Participants

The 73 right-handed patients had been enrolled in a prospective longitudinal investigation of PPA. They were selected from a set of 126 patients on the basis of 2 inclusion criteria: Western Aphasia Battery–Revised¹⁸ Aphasia Quotient (WAB-R-AQ) of 80 or above and the availability of quantitative maps of regional cortical thinning. The AQ cutoff was chosen to exclude patients whose aphasia had progressed beyond the stage where selective and dissociated impairments of language domains could be identified.

The PPA diagnosis was made by the same neurologist (M.-M.M.). A second set of tests led to a quantitative evaluation of word comprehension, object naming, sentence comprehension, grammar, and the ability to repeat phrases and sentences. The group contained 38 male participants and 35 female participants. Mean age at the time of assessment was 65.2 years with a range of 48–83; symptom duration had a mean of 3.6 years. According to a slightly modified form of the 2011 classification guidelines,^{19,20} the PPA type was agrammatic in 27, semantic in 18, logopenic in 22, and mixed or unclassifiable in 6. On all 6 language tasks, the group of 73 participants with PPA had a broad range of performance from distinctly impaired to preserved (table).

Language assessment

Word comprehension was tested with a subset of 36 moderately difficult items (157–192) of the Peabody Picture Vocabulary Test (PPVT-IV).²¹ Although the PPVT-IV is a word–picture matching task, fewer than half of the items represent concrete objects. The majority of the remaining items (e.g., salutation, perplexed, culinary) require extensive conceptual interpretation (i.e., comprehension) of the words. The Boston Naming Test (BNT) was used to assess the naming of objects.²²

Sentence comprehension was assessed with noncanonical items of the Sentence Comprehension Test of the Northwestern Assessment of Verbs and Sentences.²³ The verbs and nouns used in the test of sentence comprehension (boy, girl, dog, cat, kiss, chase) were of high enough frequency to be understood by all participants so that poor performance indicated a specific impairment in the comprehension of sentence structure.

Production of grammatically correct sentences was assessed by asking the participants to construct 30 sentences from the Northwestern Anagram Test (Thompson, Weintraub, & Mesulam, 2011, flintbox.com/public/project/9299) and by calculating the percentage of grammatically correct sentences in a recorded narrative of the Cinderella story.²⁴ Repetition of phrases and sentences was tested with the 6 most difficult items of the WAB Repetition subtest.²⁴

Controls of similar ages and education levels performed all of the tests with accuracy levels of 98% or higher and produced sentences that were grammatically correct in more than 90% of instances.²⁴

Table Demographic and performance data for the group of patients with primary progressive aphasia

	No. of patients with the relevant data	Mean (SD)	Range
Age at assessment, y	73	65.2 (7.1)	48–83
Symptom duration	73	3.6 (2)	1–10
WAB-AQ (maximum 100)	73	89.1 (4.9)	80–97
PPVT (maximum 36)	71	30.1 (7.5)	7–36
BNT (maximum 60)	73	40.4 (18.7)	4–59
REP (maximum 66)	73	53.9 (8.5)	29–66
NAT (maximum 30)	67	25.4 (4.4)	7–30
Sentence comprehension (maximum 15)	69	13.9 (1.7)	8–15
% Grammatically correct sentences (maximum 100)	66	75.6 (19.7)	9–100

Abbreviations: AQ = Aphasia Quotient; BNT = Boston Naming test; NAT = Northwestern Anagram Test; PPVT = Peabody Picture Vocabulary Test; REP = repetition task based on difficult items of the Western Aphasia Battery; WAB = Western Aphasia Battery.

Imaging

Structural MRI scans were acquired at Northwestern University's Center for Translational Imaging with a 3.0T Siemens (Munich, Germany) TIM Trio scanner and were reconstructed with the FreeSurfer image analysis suite (version 5.1) including correction of geometric inaccuracies and topologic defects using validated methods as previously described.^{25,26} Since the principles of clinico-anatomic correlations are not expected to vary by subtype and to maximize statistical power, all patients with PPA were grouped together for the imaging analyses. The regions of interest (figure 1) were constructed on the native brain surface using parcellations from the Desikan-Killiany and Destrieux atlases.^{27,28} Cortical thickness and volume maps of the patients with PPA were statistically contrasted against 38 right-handed age- and education-matched neurologically healthy volunteers. 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 PPA compared to controls.²⁹ Association between language task and cortical thickness in each of the 4 anatomical sectors was assessed using nonparametric Spearman correlations. In addition, partial correlations were performed to measure the associations of the middle temporal (MT) sector while removing the effects of adjacent regions of interest (ROIs). All tests were conducted in SPSS (SPSS Inc., Chicago, IL) version 24.0 and missing values were accounted for with pairwise deletion.

Anatomical ROI

Four ROI were identified (figure 1). (1) All 3 components of the inferior frontal gyrus (IFG) (orbitalis, triangularis, and opercularis) were combined into a single sector containing the Broca area (IFG-B). (2) The supramarginal (SG) and angular (AG) gyri of the inferior parietal lobule and the posterior third of the STG, the superior temporal sulcus, and

the MTG were combined into a single temporoparietal sector encompassing even the most extensive boundaries of the Wernicke area (PT-W). The primary auditory cortex (Heschl gyrus) was not included in this sector. (3) The middle thirds of the superior, middle, and inferior temporal gyri (STG, MTG, ITG) and the intervening sulcal cortices were combined into an MT sector. (4) The remaining anterior parts of these 3 gyri and sulci and the temporal pole were combined into an AT sector. These sectors are too large and heterogeneous to represent uniform functional territories. Nonetheless, the magnitude of each is comparable to the size of lesions seen in patients with Wernicke aphasia.^{3,13} Furthermore, the segmentation of the temporal lobe perpendicular to its long axis reflected the known posterior-to-anterior organization of information processing pathways that link word-form percepts to multimodal associations.³⁰

Neuropathology

For the autopsy case, tissue handling, staining procedures, and diagnostic criteria were identical to the methodology that was used in previous postmortem investigations of PPA.³¹

Standard protocol approvals, registrations, and patient consent

The study was approved by the Institutional Review Board of Northwestern University and informed consent was obtained from all participants. The study is listed on trials.gov with identifier NCT00537004 (clinicaltrials.gov/ct2/show/NCT00537004).

Data availability

All data are reported in the article.

Results

All 4 regions showed significant cortical thinning and volume loss in the patient group. Mean volume loss, computed in comparison to volumes in the controls, was highest in AT

Figure 1 Atrophy–function correlations within 4 components of the language network

(A) Volume loss (mean [SD]) at false discovery rate ≤ 0.05 in the group of 73 patients with PPA compared to 38 neurologically healthy controls. Red and yellow patches show significant areas of volume loss. The numbers refer to mean changes in volume and SD. Significance is displayed as a p value. (B) Significant positive correlations between cortical thinning and language tasks. The numbers in parentheses indicate r values. AG = angular gyrus; AT = anterior temporal sector; BNT = Boston Naming Test; GRAM = % grammatically correct sentences in narrative; IFG = inferior frontal gyrus; IFG-B = inferior frontal gyrus, containing the Broca area; ITG = inferior temporal gyrus; MT = mid-temporal sector; MTG = middle temporal gyrus; PPVT = Peabody Picture Vocabulary Test; PT-W = parietotemporal sector encompassing the Wernicke area; REP = repetition task based on difficult items of the Western Aphasia Battery; SMG = supramarginal gyrus; STG = superior temporal gyrus; TP = temporal pole.

(28.4%), least in IFG-B (9.6%), and intermediate in MT (20.3%) and PT-W (14.5%) (figure 1A).

Correlations of cortical thinning with performance in language tasks

Each ROI had a selective profile of positive correlations (Spearman) between cortical thinning and impairment in language tasks (figure 1B). In the IFG, where the Broca area is located, thinning was correlated with the percent of grammatically correct sentences (GRAM) ($r = 0.25$, $p = 0.041$). In the PT-W sector, where the Wernicke area is located, the only significant correlation was with performance in the repetition task ($r = 0.42$, $p = 0.001$). There was no significant correlation with PPVT ($r = -0.072$, $p = 0.553$). Thinning in MT and AT

was correlated with naming (measured by the BNT) and word comprehension (measure by the PPVT). The correlation coefficients were higher in AT for BNT ($r = 0.78$, $p < 0.001$) and for PPVT ($r = 0.60$, $p < 0.001$) than in MT ($r = 0.71$, $p < 0.001$ for BNT and $r = 0.51$, $p < 0.001$ for PPVT). No other significant positive correlations were detected. Except for the correlation of GRAM with IFG, all other correlations remained significant when corrected for multiple comparisons.

Our longitudinal investigation of cortical thinning in 126 patients with PPA had shown that the MT region is almost never an initial site of peak atrophy.³² The cortical thinning in this region tends to represent an extension from the temporoparietal or AT areas. In the present study, therefore, we conducted Spearman partial correlation analyses to explore the extent to which correlations of MT thinning with naming and word comprehension reflected atrophy in the adjacent PT-W and AT sectors. The MT cortical thinning relationships with naming and comprehension remained just as strong when the effect of PT-W atrophy was removed but disappeared when the effect of AT atrophy was removed.

We delineated the PT-W sector (green area in figure 1B) to encompass even the most inclusive mapping of the Wernicke area, which generally corresponds to the lesion sites described in patients with Wernicke aphasia. To more directly approach the question of whether any part of PT-W, especially pSTG, is critical for word comprehension, we performed a vertex-based cortical thickness correlation analysis within the combined territory of AT, MT, and PT-W with performance on the repetition task and then with the PPVT at FDR = 0.05. The correlations of PPVT were confined to the AT and MT territories. There were no significant correlations of PPVT with cortical thickness in any area that could possibly be considered to belong to the Wernicke area, including pSTG (figure 2). In contrast, there were significant correlations of repetition and thickness in posterior STG and parts of the adjacent AG and SG (figure 2). The correlations of PPVT were confined to the AT and MT territories.

Effect of cortical pathology in the Wernicke area of a patient who came to autopsy

Volume loss offers a global marker of neurodegeneration but does not reveal its cellular components. One patient who was part of our prospective PPA program died 6 months after his final testing and offered a unique opportunity for characterizing the cellular pathology in the Wernicke area and assessing its influence on word comprehension (figures 3 and 4).

At age 56, the patient started to experience progressive difficulties with word finding. The initial examination, 2 years after onset, established the diagnosis of logopenic PPA. Comportment, explicit memory for recent events, and visuospatial skills were relatively preserved by history and examination. Although word-finding impairments were quite prominent during conversation, deficits on formal testing were mild, his WAB-R-AQ was 86.9, and quantitative MRI showed

Figure 2 Atrophy–function correlations computed by individual vertex rather than by region of interest within all relevant temporoparietal cortices

Yellow and red areas show regions of significant correlations of cortical thinning (atrophy) with language comprehension and repetition scores. False discovery rate threshold was set at 0.05. AT = anterior temporal sector; MT = mid-temporal sector; MTG = middle temporal gyrus; PPVT = Peabody Picture Vocabulary Test; PT-W = parietotemporal sector encompassing the Wernicke area; STG = superior temporal gyrus.

essentially no atrophy within the components of the language network at the FDR of 0.05. Two years later, there was substantial worsening of object naming (scores declining from 90% to 32%) and repetition (scores declining from 85% to 41%). However, word comprehension remained relatively intact (97% at the first visit and 89% at the second) (figure 3B). At the second testing, 6 months before death, the temporoparietal regions encompassing the Wernicke area (PT-W) had a 48.6% volume loss when compared to control values (figure 3A). The atrophy at that time also extended into parieto-occipital cortex but was not detectable in the other 3 ROIs in figure 1.

He died at age 61, 6 months after the second evaluation. At autopsy, the brain weighed 1,250 g. The neuropathologic examination showed a Braak & Braak neurofibrillary degeneration stage of VI and a Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque score of C, leading to a primary diagnosis of Alzheimer neuropathology as the cause of the PPA (figure 4, A and B).

Quantitation of neurofibrillary tangles (NFT) in this case had been done for another study.³³ According to density counts established by unbiased stereology, the left hemisphere pSTG

and SG components of the Wernicke area had the highest NFT densities, at around 25,000/mm³ (figure 3C), while other cortical components such as IFG had much lower counts. There was an asymmetric NFT density favoring the language-dominant left hemisphere and higher NFT densities in neocortical areas such as pSTG and SG when compared to memory-related limbic areas such as entorhinal cortex. The cortex within pSTG and SG displayed severe neurodegeneration manifested by gliosis, disruption of normal cytoarchitecture, and decreased density of neurons (figure 4, C and D). Considering the temporal progression of Alzheimer disease, which takes decades to reach its terminal stages, it is likely that the severe pathology delineated at autopsy was also present at the second language assessment 6 months before death.

Discussion

The variability of the boundaries proposed for the Wernicke area and the controversies surrounding its relevance to language comprehension have prompted recent calls to eliminate the usage of this eponym altogether.³⁴ However, the term Wernicke area is so entrenched in the literature that such recommendations, while rational, are unlikely to be adopted. The goal of the current study was not to rediscover or redefine the location of the Wernicke area, an enterprise that may be of great historical interest but not particularly productive for exploring the neurobiology of language. Instead, we aimed to investigate the differential sensitivity of word comprehension to cortical damage along a rostrocaudal axis of temporal neocortex, an axis that incorporates association pathways linking unimodal percepts, such as word forms, to corresponding transmodal associations that mediate their recognition as concepts.³⁰ The posterior part of this axis, PT-W of figure 1, represents a composite of arguably all sites that have been proposed over the years as components of the Wernicke area.

In the group of 73 patients with PPA who participated in this study, word comprehension impairment showed no significant correlation with cortical thinning (i.e., volume loss) within the parietotemporal cortices that encompass even the most expansive delineation of the Wernicke area (PT-W in figure 1). A second analysis by individual vertex rather than entire ROI showed that the absence of correlation with comprehension characterized atrophy not only in PT-W as a whole but also in its individual components such as pSTG, SG, AG, and pMTG (figure 2). Furthermore, the postmortem examination of a patient with PPA showed that severe neuronal degeneration in this region may leave word comprehension essentially intact. The strongest anatomical correlates of word comprehension were located anterior to PT-W, particularly within the rostral third of the temporal lobe. These results are in keeping with most prior investigations on PPA and semantic dementia but in conflict with classic principles of aphasiology and some of its current reformulations.

Figure 3 Cortical thinning map in a patient with primary progressive aphasia (PPA) obtained 6 months before death

Our failure to implicate the Wernicke area in word comprehension could be questioned by pointing out that residual neurons might have sustained performance on the PPVT. Although regions of even severe atrophy may still contain neurons that appear intact,²⁰ 2 considerations can be offered to counter this objection. First, PT-W atrophy was correlated with impairment of repetition. It is difficult to see why residual neurons of PT-W would selectively support comprehension but not repetition. Second, in the 1 patient where the cellular basis of PT-W atrophy could be quantitated by microscopic analysis, severe neuronal degeneration in the pSTG and SG components of the Wernicke area impaired repetition but not word comprehension. Although the null hypothesis is always difficult to prove, this evidence strongly suggests that word comprehension is not particularly sensitive to the integrity of PT-W and, therefore, of the Wernicke area.

The PT-W sector in this study included the posterior third of the STG but not the primary auditory cortex of Heschl gyrus. According to DeWitt and Rauschecker's³⁵ meta-analysis, the STG contains an anteriorly directed synaptic hierarchy that links auditory input first to a region selectively tuned to phonemes and then to an area specialized for transforming phonemes into auditory word forms. The absence of correlation between auditory word comprehension and PT-W atrophy suggests that the pivotal word form areas are located more anteriorly, possibly within the MT sector, and that the input they receive from upstream auditory areas, originating in Heschl gyri of both hemispheres, remains preserved.

Repetition of phrases and sentences was the 1 function most sensitive to cortical abnormalities of PT-W, and specifically its posterior STG component. This relationship is in keeping with investigations on stroke-induced conduction aphasia and logopenic PPA, showing that the parietotemporal junction is crucial for the integrity of phonologic encoding and auditory working memory.^{5,6,10,36,37} Regression analyses had previously shown that impairments in the comprehension of syntactically complex sentences are correlated with cortical thinning in the IFG as well as the SG and AG components of PT-W.³ Since the current investigation did not find a correlation between sentence comprehension impairment and volume loss in PT-W, compromise of this function may be contingent on injury not only within the Wernicke area but also within frontal components of the language network.

The large-scale network model posits that each network node mediates critical (or essential) as well as ancillary (or sustaining) functions related to its principal cognitive domain.^{30,38} While initial stages of damage to a given node may not cause fixed impairments of its ancillary functionalities, the overall computational flexibility of the network for mediating that task may be compromised. Such disruptions in domains of ancillary functionality can be detected by tasks that impose heavy computational loads. These principles apply to the role of the Wernicke area in language comprehension. For example, patients with agrammatic and logopenic PPA whose atrophy tends to be concentrated in PT-W and who have normal PPVT scores display abnormally prolonged semantic interference effects and loss of the N400 semantic incongruence potential.^{39,40} Furthermore, fMRI investigations

(A, B) Thioflavin-S histofluorescence in layer 5 of the supramarginal gyrus (SMG) and posterior STG of the patient with PPA. Magnification $\times 200$. (C) Cresylviolet stain of posterior superior temporal gyrus (STG) from the autopsy of a 54-year-old neurologically intact person shows pyramidal neurons (arrows) organized in columnar fashion. Magnification $\times 100$. (D) Cresylviolet stain from posterior STG in the patient with PPA shows gliosis, angulated pyknotic neurons, and loss of columnar architecture. Magnification $\times 100$.

using synonym identification tasks revealed activations not only in the AT sector but also in posterior temporal cortex.^{41,42} It appears, therefore, that parietotemporal cortex where the Wernicke area is located has an ancillary but not essential role in single word comprehension. In fact, single case studies show that an intact Wernicke area cannot sustain word comprehension in patients with AT atrophy.⁴³ The decline of BNT scores on the second but not initial examination of our PPA patient who came to autopsy (figure 3) also suggests that extensive atrophy in the Wernicke area does

eventually interfere with the lexicosemantic task of object naming. However, object naming appears less sensitive to neurodegeneration in the Wernicke area than repetition and also more dependent on the integrity of AT cortices.

We found a strong correlation between atrophy of the AT and impairment on the PPVT. This correlation suggests that word comprehension is an essential function of AT cortex, a conclusion that is consistent with previous work on PPA, semantic dementia, and herpes simplex encephalitis.^{14,15,43–45}

The critical role for word comprehension attributed to the AT sector is also consistent with more recent reports based on multimodal functional mapping of language and principal component analyses in patients with stroke.^{10,35} This relationship was neither detected nor suspected by classic aphasiology, probably because AT is not susceptible to focal cerebrovascular lesions. The area we delineated as AT is heterogeneous and includes the temporal pole as well as the anterior components of STG, MTG, and ITG. It should be pointed out that the anterior fusiform and parahippocampal gyri, which may also play important roles in comprehension,^{43,46} were not included in any of the sectors involved in these analyses. Although the results in this report are confined to the left hemisphere, our previous work had shown that unilateral left AT lesions are sufficient to cause severe word comprehension impairments so that the association of this region with comprehension impairment is not necessarily related to its known propensity for bilateral degeneration.⁴³

Object naming and word comprehension impairments were also associated with atrophy in the mid-sectors of the temporal lobe (MT in figure 1). This association deserves a cautious interpretation. MT is rarely, if ever, the initial site of peak atrophy in PPA. Atrophy spreads into this region either from AT (in semantic PPA) or from PT-W (in logopenic PPA).³² Even when MT is a site of peak atrophy, word comprehension remains unaffected if AT is not also atrophied.³ We therefore conducted additional analyses and found that the MT relationships with naming and comprehension remained just as strong when the effect of PT-W atrophy was factored out but disappeared when the effect of AT atrophy was factored out. The correlation of MT atrophy with word comprehension and naming impairments may therefore be contingent on the extension of neurodegeneration from AT in the course of disease progression.

We have seen patients where AT atrophy was associated with severe deficits of object naming in the absence of additional word comprehension impairments. In some of these patients, word comprehension impairments emerged when the peak atrophy spread posteriorly into the MT.³ It is therefore conceivable that word comprehension is most consistently impaired when AT and MT are both damaged. In some cases, AT atrophy alone seems sufficient to undermine word comprehension but we have not seen cases where isolated MT atrophy (or anterior extension of atrophy from PT-W to MT) has been associated with such deficits. This formulation helps to explain why left AT lobectomy can lead to naming but not necessarily comprehension impairment as lobectomies rarely extend into MT.⁴⁷ Several recent models of the language network have emphasized the key role of the MTG for word comprehension.^{6,11,12,48,49} The critical part of the MTG identified in many of these models is located posteriorly and falls within the PT-W sector of figure 1. In others, it does extend more anteriorly into the MT sector of figure 1. Our results suggest that mid-MTG damage influences word comprehension but that this may become clinically

consequential only in the presence of additional destruction (or perhaps disconnection) of cortices within the AT sector.

Nearly all contemporary textbooks of neurology, more than a century of classic aphasiology, and several current lesion-symptom mapping studies state that language comprehension is linked to the integrity of parietotemporal regions where the Wernicke area is located. These statements cannot be dismissed lightly and need to be reconciled with our findings. An important fact to consider is that the linkage of parietotemporal cortex to comprehension is almost always based on patients with cerebrovascular rather than degenerative disease. Furthermore, the lesions tend to be large and include most of the PT-W territory rather than being confined to the pSTG or SG sectors at the core of the Wernicke area. These considerations lead to 2 models of reconciliation: one based on disconnection and the other on diaschisis (figure 5).

The reconciliation through disconnection rests on the fact that vascular territories include not only cortex but also deep white matter tracts. In the context of a stroke encompassing the PT-W sector, injury to the cortex of the Wernicke area would disrupt repetition, as predicted by the correlations in figure 2. Moreover, the additional destruction of deep white matter tracts coming from otherwise intact posterior and contralateral cortices would trigger a broader deafferentation of the language network, and might cause the word and sentence comprehension impairments characteristic of Wernicke aphasia. In contrast, degenerative injury to the cortex of the Wernicke area as seen in PPA, while also impairing repetition, would cause only a partial disconnection of the anterior language areas, insufficient to undermine comprehension. The clinical outcome would be a logopenic aphasia. Accordingly, the cortex of the Wernicke area is not all that important for word comprehension, whereas the Wernicke region is pivotal because it also lies at the confluence of deep white matter tracts, the exact identity of which remain to be determined. In keeping with this formulation, Wernicke aphasia is almost never reported in PPA, and is not part of its current classification system.¹⁹

The second potential reconciliation relies on diaschisis, which denotes a severe postsynaptic depression of neuronal activity that transcends the effect of simple disconnection. Diaschisis can be transient, as in spinal shock, or permanent, as in the case of crossed cerebellar atrophy. A stroke in the Wernicke area could elicit word comprehension impairments through diaschisis in the AT sector, explaining why the most consistent relationship of the Wernicke area to Wernicke aphasia has been reported in the acute stages of cerebrovascular accidents. In fact, clinical experience shows that stroke-induced Wernicke aphasia frequently resolves into conduction aphasia in the chronic stage as diaschisis is resolved and as the cortical dysfunction of the Wernicke area becomes the defining substrate of the aphasia. In neurodegenerative disease, however, the indolent pace of neuronal injury precludes diaschisis and therefore word comprehension remains relatively preserved.

Figure 5 Two models for reconciling lesion-symptom relationships of the Wernicke area in neurodegenerative vs cerebrovascular lesions

Double-headed arrows illustrate projection pathways. Red denotes destruction or severe functional loss; pink indicates partial functional disruption; green indicates sparing. The blue striped bars indicate destruction of the underlying projection pathway. AT = anterior temporal region; BR = Broca area; WER = Wernicke area.

It is also worth considering the possibility that the indolent pace of neuronal loss in PPA may have triggered synaptic reorganization elsewhere in the network. Functions normally mediated by the Wernicke area could therefore have shifted to other cortical regions. This possibility cannot be ruled out but is unlikely for 2 reasons. First, it would be difficult to envisage a mechanism of reorganization that would spare word comprehension but not repetition upon destruction of neurons in the Wernicke area. Second, the phenomenon would have to be unique to the Wernicke area since a similar process of compensatory reorganization does not seem to relieve the word comprehension impairment of AT atrophy or the agrammatism of IFG atrophy. Nonetheless, the question of synaptic reorganization in neurodegenerative diseases deserves further investigation. Such processes have been demonstrated in PPA but whether they represent aberrant rewiring or compensatory reorganization remains to be resolved.^{42,50}

Quantitative atrophy–deficit correlations in PPA are converging toward the view that the cortical neurons of the

Wernicke area (defined broadly as the PT-W sector or narrowly as pSTG) play an ancillary rather than critical role in word comprehension and that the principal contribution of this area in the language domain is to mediate phonologic encoding and repetition. The function of word comprehension, once linked to the Wernicke cortex, is moving to more anterior parts of the temporal lobe. This historic shift in the organization of the language network can potentially be reconciled with classic aphasiology by considering the physiologic and hodologic differences between the effects of stroke and those of neurodegeneration.

Author contributions

M.-M. Mesulam: study concept and design. B.M. Rader: acquisition and summaries of data. J. Sridhar: acquisition of data, preparation of images in figures. M.J. Nelson: critical revision of the manuscript and intellectual content. J. Hyun: critical revision of the manuscript and intellectual content. A. Rademaker: data analysis and critical revision of the manuscript and intellectual content. C. Geula: neuropathologic images and data summary, critical revision of the manuscript and

intellectual content. E.H. Bigio: neuropathologic images and data summary, critical revision of the manuscript and intellectual content. C.K. Thompson: critical revision of the manuscript and intellectual content. T.D. Gefen: neuropathologic images and data summary, critical revision of the manuscript and intellectual content. S. Weintraub: critical revision of the manuscript and intellectual content. E. Rogalski: image analysis and critical revision of the manuscript and intellectual content.

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Disclosure

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