The Wernicke conundrum revisited: evidence from connectome-based lesion-symptom mapping

William Matchin[1]*, Dirk-Bart den Ouden[1], Gregory Hickok[2], Argye E. Hillis[3], Leonardo Bonilha[4], Julius Fridriksson[1]

Abstract

The classical assumption that Wernicke's area supports word and sentence comprehension has been questioned following discrepant results in primary progressive aphasia. We tested the hypothesis of Mesulam et al. (2015; 2019) that word and sentence comprehension deficits in stroke-based aphasia result from 'double disconnection' of both anterior temporal lobe and inferior frontal lobe to temporoparietal cortex due to white matter damage, rather than dysfunction of Wernicke's area itself. We performed lesion-deficit correlations, including connectome-based lesion-symptom mapping, in four large, partially overlapping groups of English-speaking chronic left hemisphere stroke survivors. After removing variance due to object recognition and associative semantic processing, the same middle and posterior temporal lobe regions were implicated in both word comprehension deficits and complex noncanonical sentence comprehension deficits. Connectome lesion-symptom mapping revealed similar temporal-occipital white matter disconnections for impaired word and noncanonical sentence comprehension, including the temporal pole. We found additional significant temporal-parietal disconnections for noncanonical sentence comprehension deficits, which may indicate a role for phonological working memory in processing complex syntax, but no significant frontal-temporal or frontal-parietal disconnections. In addition, damage to these middle-posterior temporal lobe regions was associated with both word and noncanonical sentence comprehension deficits even when accounting for variance due to the relevant white matter disconnections. Our results largely agree with the classical notion that Wernicke's area, defined here as middle superior temporal gyrus and middle-posterior superior temporal sulcus, supports both word and sentence comprehension, suggest a supporting role for temporal pole in both word and sentence comprehension, and speak against the hypothesis that comprehension deficits in Wernicke's aphasia result from double disconnection.

[1]Dept. of Communication Sciences and Disorders, University of South Carolina
[2]Dept. of Cognitive Sciences, Dept. of Language Science, University of California, Irvine
[3]Dept. of Neurology, Johns Hopkins University School of Medicine and Dept. of Cognitive Science, Johns Hopkins University
[4]Dept. of Neurology, Medical University of South Carolina

*Corresponding author

915 Greene St., Discovery 1, Room 202D, Columbia, SC 29208, USA
Email: matchin@mailbox.sc.edu
Tel: +1 803-777-9240

Running Title: The Wernicke conundrum revisited

Keywords: aphasia; lesion-symptom mapping; connectome; word comprehension; noncanonical sentence comprehension; syntax; stroke; Wernicke's area

1 Introduction

The classical model of language in the brain posits a primary role for Wernicke's area, roughly thought to be the posterior superior temporal lobe and inferior parietal lobe (with definitions varying widely)[1–3], in both word and sentence comprehension [4–7], defined as a set of processes involving the transformation of an auditory signal onto linguistic representations at the lexical and syntactic levels[8]. The major motivation for the primacy of Wernicke's area in word and sentence comprehension is the notable comprehension deficits in Wernicke's aphasia, typically involving posterior temporal-parietal damage [9,10], which roughly corresponds to the region classically associated with Wernicke's area [2,3].

Recently, the classical view has been questioned from the perspective of primary progressive aphasia (PPA). Mesulam et al.[1] performed a voxel-based morphometry (VBM) study in 72 people with PPA on word and sentence comprehension. Their sentence comprehension task minimized lexical access demands by using sentences with highly frequent words (e.g., boy, girl, dog, cat, kiss, chase) and noncanonical structures (object-first sentences such as passives, which do not conform to expected word order), to emphasize grammatical processing. By contrast, their word comprehension task (PPVT) maximized lexical-semantic demands, and the variance due to object recognition and non-verbal semantics was factored out using the Pyramids and Palm Trees test[11] (PPT) as a covariate. They found no association of posterior temporal-parietal atrophy with word comprehension deficits and minimal association of atrophy in this region with deficits in noncanonical sentence comprehension. By contrast, atrophy of the anterior temporal lobe (ATL), primarily the temporal pole, was strongly associated with word comprehension (but not sentence comprehension) impairment, whereas inferior parietal and frontal degeneration was associated with sentence comprehension (but not word comprehension) impairment. Mesulam et al.[12] followed up this study by showing that repetition (but not word comprehension) was associated with degeneration of superior posterior temporal and inferior parietal lobes. Overall, they associated the temporal-parietal territory commonly attributed to Wernicke's area with a phonological working memory function, not critical for basic aspects of linguistic processing.

To explain the discrepancy of their results with the literature on Wernicke's aphasia, Mesulam et al.[1] posited a "double disconnection" hypothesis. Given that strokes often impinge on white matter, and that disconnection due to white matter damage can impair language abilities independently of cortical grey matter damage [13,14], they suggested that lesions to temporal-parietal cortex may impair both word and sentence comprehension, not through damage to the relevant cortical centers themselves but through disconnection [15]. In light of their VBM results in PPA, they proposed that the ATL is the key region underlying word comprehension and that frontal cortex (primarily Broca's area or the posterior two thirds of the inferior frontal gyrus, IFG) is the key region for sentence/syntactic processing, both of which may be disconnected due to posterior temporal-parietal strokes.

There are two problems with this logic. First, functional neuroimaging studies have shown that the spatial location and extent of activation of syntactic processing and lexical access are remarkably similar (for meta-analyses and reviews, compare Hagoort & Indefrey[16] for syntactic processing and Lau et al.[17] for lexical access). This reliably includes the posterior superior temporal sulcus (STS) and posterior middle temporal gyrus (MTG), falling within the traditional Wernicke's territory, among other regions, including prominently the IFG, ATL, and inferior angular gyrus. Regardless of the explanation for this overlap [18,19], these activations should be accounted for via some functional mechanism, and suggests (though does not prove) a functional role in comprehension.

Second, a large body of LSM studies in post-stroke aphasia have shown that damage to Broca's area and surrounding areas is not reliably implicated in sentence or syntactic comprehension deficits [20–25]. There may be a minor supporting role for frontal cortex in supporting the processing of particularly difficult sentence structures[26], although the location of the lesion correlates of such deficits is inconsistent [20,27–30] (for a review, see Matchin & Hickok[19]). If noncanonical sentence comprehension deficits in Wernicke's aphasia are primarily due to disconnection of Broca's area/posterior IFG from the rest of the language network, then one would expect frontal lesions to also impair syntactic comprehension. However, this is not a pattern that is reliably seen, in contrast to that associated with posterior temporal-parietal damage, which reliably predicts sentence comprehension impairments [20,21,23,24,28,29,31].

For these reasons, the dissociation, both in behavior and lesion correlates, between word and sentence comprehension in PPA reported by Mesulam et al.[1] is surprising and deserves scrutiny. We examined these issues, testing the hypothesis of Mesulam et al. that overlap of word and sentence comprehension deficits in post-stroke aphasia is due to distinct disconnection patterns. We analysed data in a large group of people with post-stroke aphasia using LSM as well as connectome-based lesion-symptom mapping (CLSM), which uses diffusion tensor imaging to ascertain the strength of white matter connections between regions associated with behavioral scores [32–34]. In a previous report [32], our research group performed LSM and CLSM analyses of word comprehension alone (with PPT as a covariate) in a smaller group of subjects (43), finding that impaired word comprehension was associated with damage to the inferior temporal gyrus and disconnection between posterior middle temporal gyrus and inferior temporal gyrus. A follow-up study[8] expanded the number of subjects (99) and performed LSM analyses, finding the most robust association of word-level deficits (with PPT as a covariate) with damage to middle-posterior superior temporal gyrus (STG) and STS.

Here we expand the number of subjects further and add several behavioral measures to directly compare our results to Mesulam et al., crucially including a measure of noncanonical sentence comprehension and CLSM analyses. We predicted that both word and noncanonical sentence comprehension would primarily involve damage to the middle-posterior temporal lobe and similar disconnection patterns throughout the temporal lobe, and that damage to these areas would predict comprehension impairments above and beyond the contribution of the relevant disconnection patterns. We expected a possible implication of parietal damage and/or disconnection in noncanonical sentence comprehension due to phonological working memory demands that are strongly associated with parietal areas [35–38].

2 Materials & Methods

2.1 Subjects and measures

We performed behavioral and lesion mapping analyses in four partially overlapping groups of English-speaking subjects (Table 1). We collected anatomical images and created lesion maps for all subjects, but diffusion tensor data for our CLSM analyses was unavailable for several subjects. Group 1 consisted of 218 subjects (199 included in CLSM) who were assessed on the Western Aphasia Battery-Revised [39], with subsets of this group being assessed on a variety of other measures. Group 2 consisted of a subset of 180 subjects (167 included in CLSM) who were assessed on the Pyramids and Palm Trees test [11]. Group 3 consisted of a subset of 130 subjects (127 included in CLSM) who were assessed on one of two similar assessments of sentence comprehension ability involving picture-matching and a variety of semantically reversible canonical and noncanonical sentence structures, the Sentence Comprehension Test subset of the Northwestern Assessment of Verbs and Sentences (NAVS) [40] (N = 82) or a task which we label here the Icelandic Task (since its translation was first used in a sample of Icelandic stroke survivors with aphasia[29,41] (N = 48). Finally, Group 4 consisted of a subset of 92 subjects (90 included in CLSM) who were evaluated for expressive agrammatism using consensus perceptual ratings of spontaneous speech samples in one of two studies, Den Ouden et al.[42] (N = 39) or Matchin et al.[43] (N = 53).

Table 1 Subject demographic data

	Group 1	**Group 2**	**Group 3**	**Group 4**
Measures	Western Aphasia Battery-Revised	Pyramids and Palm Trees	Noncanonical Sentence Comprehension	Perceptual Ratings of Expressive Agrammatism
Total number of subjects	N = 218 (199 included in CLSM)	N = 180 (167 included in CLSM)	Total N = 130 (127 included in CLSM) Icelandic task: N = 48 NAVS: N = 82	Total N = 92 (90 included in CLSM) Den Ouden et al. (2019): N = 39 Matchin et al. (2020): N = 53
Sex	133 Male, 85 Female	112 male, 68 female	83 male, 47 female	60 male, 32 female
Mean age at testing (years)	60.3 (SD = 11.4)	60.5 (SD = 11.4)	60.0 (SD = 10.7)	58.7 (SD = 11.3)
Mean months post-first stroke at initial testing	42.6 (SD = 48.3)	41.2 (SD = 47.6)	45.3 (SD = 50.4)	45.6 (SD = 48.5)
Mean number of strokes	1.2 (SD = 0.5)	1.2 (SD = .5)	1.2 (SD = 0.5)	1.1 (SD = 0.4)
Mean education (years)	15.0 (SD = 2.3), *N = 210	15.0 (SD = 2.3), *N = 175	15.4 (SD = 2.4), *N = 128	15.3 (SD = 2.4)
Mean lesion volume (mm^3)	120,855 (SD = 97,488)	128,446 (SD = 97,036)	111,267 (SD = 92,645)	96,175 (SD = 84,514)
Mean WAB-R AQ	61.4 (SD = 28.1)	60.0 (SD = 26.6)	65.3 (SD = 26.9)	75.8 (SD = 19.9)
Mean WAB-R Auditory Word Recognition	50.0 (SD = 13.2)	49.8 (SD = 12.9)	51.0 (SD = 12.7)	54.7 (SD = 9.0)
Mean WAB-R Sequential Commands	51.4 (SD = 23.5)	50.4 (SD = 22.5)	54.5 (SD = 22.7)	61.0 (SD = 19.5)
Mean WAB-R Repetition	5.5 (SD = 3.4)	5.3 (SD = 3.3)	5.9 (SD = 3.3)	7.0 (SD = 2.7)

SD = standard deviation. AQ = aphasia quotient of the WAB-R, a summary measure of overall language ability; WAB-R = Western Aphasia Battery-Revised; SD = standard deviation. *education information was not available for all subjects, the number for which education information indicated here.

All subjects provided informed consent to participate in this study, which was approved by the Institutional Review Boards at the University of South Carolina and the Medical University of South Carolina. All subjects were native speakers of American English and had at least one ischemic stroke to the left hemisphere at least six months prior to study inclusion.

In order to compare our study effectively with the studies of Mesulam et al. in PPA[1,12], we included a similar set of six behavioral measures: the WAB-R Auditory Word Comprehension subtest, the Pyramids and Palm Trees Test (PPT), the Philadelphia Naming Test, Noncanonical Sentence Comprehension, the WAB-R Repetition subtest, and our perceptual ratings of Expressive Agrammatism. Each of these measures is described below. Out of these six measures, we ultimately performed four lesion mapping analyses, described in section 2.3.

The Auditory Word Recognition subtest of the WAB-R [39] involves asking the subject to point to real-world objects or printed images (n = 60). Importantly, the test does not require syntactic parsing in order to perform correctly, as the subject only needs to identify the lexical item presented in each item. Our *Word Comprehension* measure used for lesion analyses consisted of this measure incorporating the Pyramids and Palm Trees (PPT) measure described below as a covariate.

The WAB-R Repetition subtest [39] (referred to subsequently as *Repetition*) involves presenting a series of increasingly more complex utterances and requiring subjects to repeat them verbatim. Scoring is based on the number of words correctly recalled in the correct order.

The Pyramids and Palm Trees test (PPT) [11] involves presenting a target picture with two candidate pictures below that are possible associates of the target picture (e.g., the target picture could be a pyramid, with candidate pictures of palm trees and pine trees). The subject is required to point to the candidate picture that is more related to the target picture (e.g. the palm trees). There are a total of 52 trials. This task was included in order to provide a control for object recognition and non-verbal semantic processing in the WAB-R word comprehension test (as in Mesulam et al.[1] and Bonilha et al.[32]).

The Philadelphia Naming Test (PNT) [44] is a 175-item assessment of picture naming, involving the presentation of a number of simple line drawings. Here we used the total number of items correctly named on the task (rather than phonological or semantic errors).

Our *Noncanonical Sentence Comprehension* measure was derived from either the NAVS (N = 82) or the Icelandic task (N = 48). The NAVS Sentence Comprehension Test [40] involves testing the comprehension of a variety of canonical and noncanonical sentence types, each with five total trials, assessed via pointing to the correct picture. Mesulam et al. (2015) assessed the comprehension performance on the three noncanonical sentence types: passives (with a by-phrase) e.g. *the dog is chased by the cat*, object-extracted WH-questions, e.g. *who is the cat chasing?*, and object-relatives, e.g. *Pete saw the boy who the girl is pulling*, for a maximum score of 15. The Icelandic task includes a similar set of canonical and noncanonical sentence types, each with five total trials: passives (with a by-phrase), e.g. *the boy is painted by the girl*, object-extracted WH-questions, e.g. *which boy is the girl painting?*, and object clefts, e.g. *it is the girl that the boy paints*. The sentence types across the two tasks are not strictly identical, but

involve essentially the same structures with the same degree of complexity, including the key factor of noncanonical object-first word order. Therefore, for subjects who were not assessed with the NAVS, we calculated the equivalent scores on the Icelandic task (correct noncanonical trials, out of 15 points).

The *Expressive Agrammatism* measure was a perceptual measure of grammatical deficits in speech production. We derived this measure from samples of connected speech production elicited either by describing the Cookie Theft picture[45] (N=39) as reported in Den Ouden et al.[42] or retelling the story of Cinderella in their own words[46] (N=53), as reported in Matchin et al.[43]. Production samples were rated independently by speech and language experts for the systematic simplification of sentence structure and omission of function words and morphemes. This resulted in a categorical assessment for each subject, either agrammatic or not.

2.2 Brain imaging and lesion mapping

We acquired anatomical MRI and DTI data using the same parameters and procedures as described in [28,32,42]. High-resolution neuroimaging data (T1- and T2-weighted images) were collected at the University of South Carolina and the Medical University of South Carolina on a 3T Siemens Trio scanner with a 12-element head coil. Lesions were demarcated onto each subject's T2 image by an expert neurologist (Dr. Leonardo Bonilha) or an expert cognitive neuroscientist (Dr. Roger Newman-Norlund) extensively trained by Dr. Bonilha (with consultation as needed with an expert on lesion mapping, Dr. Chris Rorden), both blind to the behavioral data. Lesion maps were then aligned to the high resolution T1 image. Lesions were replaced with the corresponding brain structure from the intact hemisphere, and this image as well as the lesion map in subject space were subsequently warped to MNI space using SPM12 [47]. The warped lesion map was then binarized with a 50% probability threshold, which was used to perform voxel-wise and region of interest (ROI) analyses.

Lesion overlap maps for both groups are shown in Figure 1. Overall, there was good coverage in perisylvian cortex, covering all relevant language-related regions (see lesion overlap maps in Figure 1). This included the ROIs in the JHU atlas (depicted in Figure 3)[48] which we used for lesion-symptom mapping (LSM) and connectome-based lesion-symptom mapping (CLSM) analyses. The JHU parcellation provides good alignment with language-relevant brain regions and has roughly equivalent parcel sizes relative to other parcellations such as the AICHA atlas[49]. It contains two ROIs containing the polar and lateral anterior components of the STG and MTG (STG pole and MTG pole), which correspond to key components of the ATL. We note that Mesulam et al.[1,12] define the ATL as including regions more inferior and posterior to these two ROIs. However, we also note that Mesulam et al.[1] attributed a dominant role to the polar part of the ATL, p. 2431: "…the ATL peak atrophy sites associated with severe word comprehension impairment consistently included the temporal pole…ATL neuronal loss causes major word comprehension impairments only if it extends anteriorly all the way into the polar region", thus we consider these two ROIs as well-defined to test the disconnection claim. However, as described below in section 2.3.4, we accommodated the possibility that more posterior portions of the ATL might be relevant to the disconnection claims in our combined LSM and CLSM analyses.

2.3 Analyses

2.3.1 Behavioral

To examine the relationship among the six total behavioral variables, we performed non-parametric Spearman correlations using JASP [50]. Missing data were accounted for with pairwise deletion. Non-parametric Spearman correlations were used given that the behavioral variables did not have pairwise normal distributions. Lesion volume is strongly correlated with aphasia severity in chronic stroke [51–53], including in our data (one-tailed Spearman's rho correlating WAB-R AQ and lesion volume = -0.694, $p = 6.254 \times 10^{-33}$), and therefore a potential confound [54,55], which we controlled by using lesion volume as a covariate in our LSM analyses. Similarly, we report behavioral correlations both with and without lesion volume as a covariate to evaluate overall severity effects. Mesulam et al.[1] did not correct their behavioral correlation analyses for multiple comparisons, but given the large number of behavioral correlations we performed (15 pairwise correlations without lesion volume as a covariate, 15 pairwise correlations with lesion volume as a covariate), we report whether or not each correlation survived a Bonferroni correction for multiple comparisons, treating each set of 15 correlations (with and without the lesion volume covariate) as a separate family of tests, using an adjusted alpha level of $p < 0.003$.

2.3.2 LSM

With respect to LSM, using NiiStat (https://www.nitrc.org/projects/niistat/) we performed both voxel-based and ROI-based analyses relating each of the four selected behavioral variables to lesion location. ROI analyses were included in order to maximize statistical power and afford an opportunity to combine the LSM and CLSM data to test the hypothesis of Mesulam et al. that disconnection accounts for the substantial association of damage to middle-posterior temporal lobe regions and comprehension impairments. For voxel-based analyses, we performed one-tailed t-tests within each voxel comparing the magnitude of the behavioral measure for subjects with and without damage to that voxel (results were converted to Z-values for ease of interpretation). For ROI analyses, we performed univariate linear regression analyses relating proportion damage within the grey matter of each parcellated region (the number of voxels that were damaged divided by the total number of voxels in each region) contained within the JHU atlas (depicted in Figure 3), except for Expressive Agrammatism which was logistic regression [48]. Both voxel-based and ROI-based analyses were only performed within voxels/regions that had at least 10% of subjects with damage located there [55,56] and were corrected for multiple comparisons using permutation tests (10,000 permutations) with a corrected alpha threshold of $p < 0.05$. We performed analyses for four behavioral measures that provided maximum comparison to the analyses of Mesulam et al.[1,12]: WAB-R Auditory Word Recognition with PPT as a covariate (*Word Comprehension*), *Noncanonical Sentence Comprehension*, WAB-R Repetition (*Repetition*), and *Expressive Agrammatism*. Lesion volume was included as a covariate in all LSM analyses to ensure accurate localization [54,55]. Univariate analyses were performed as opposed to multivariate approaches such as Support Vector Regression (SVR) in order to match the univariate analyses of Mesulam et al. [1], for straightforward interpretation of statistical results, and because univariate approaches have been shown to outperform multivariate approaches with large sample sizes and adequate lesion load restrictions[55]. To supplement our voxel-based analyses, we also report reduced threshold (voxel-wise $p < 0.01$) lesion maps for all

behavioral variables in order to provide the fullest picture of the lesion data without obscuring near-threshold results.

To address the question of regions that cause both word and sentence comprehension impairment, we calculated the overlap of the corrected voxel-based lesion maps for the Word Comprehension and Noncanonical Sentence Comprehension measures. Regions with significant overlap could be considered candidates for an updated anatomical definition of "Wernicke's Area" according to its functional definition as causing both of these impairments.

Finally, an additional issue concerns the fact that our Word Comprehension and Noncanonical Sentence Comprehension measures do not control for prelexical speech perception impairments. We performed analyses of two additional measures including the Repetition score as an additional covariate to attempt to control for these impairments. We first combined the behavioral scores with these covariates (WAB-R Auditory Word Recognition with both PPT and Repetition, and Noncanonical Sentence Comprehension with Repetition) and then performed LSM analyses of the two resulting measures in the same manner as described above.

2.3.3 CLSM

For CLSM, we analyzed the diffusion-weighted images that were acquired for each subject and estimated the connection strength between a subset of 27 left hemisphere and 4 right hemisphere cortical regions within the JHU atlas [48] that included the entire lateral temporal cortex, inferior parietal lobe, inferior and middle frontal lobe, and lateral and medial visual cortex of the occipital lobe (see Figure 3 for a depiction of the JHU atlas and the selected regions for CLSM analysis). Visual cortex regions were included to assess the possibility that disconnection between visual areas and language regions might underlie deficits in task performance, as both Word Comprehension and Noncanonical Sentence Comprehension require mapping an auditory speech input to pictures. First, each subject's T1 image was used to register white matter and region parcellation to the diffusion-weighted images. Next, we estimated connection strength between regions using fiber count (corrected for distance and region volume) for each of the 465 pairwise connections by using probabilistic tractography as implemented in FSL's FDT method [57], using an approach that minimizes the potential distorting effects of brain damage on to fiber tracking[13]. Pairwise connectivity was calculated as the fiber count arriving in one region when another region was seeded and averaged with the fiber count calculated in the reverse direction. The lesioned tissue was removed from all tractography tracings in order to maximize accuracy, which also minimizes the effect of lesion volume on the final analyses. The estimated number of streamlines from a completely destroyed region was set to zero. Overall, the number of streamlines that can be estimated between a pair of regions is constrained but not determined by the amount of damage to each region, as the damage to intervening white matter pathways is crucial to estimating the intact connections between these regions. The number of estimated tracts connecting pairs of regions was divided by the total volume of both regions, controlling for unequal region sizes. For full details of the methodological approach, see other publications from our research group using the same method [32,34].

We then performed linear regression analyses relating scores on each behavioral measure with the estimated connection strength for each connection using NiiStat

(https://www.nitrc.org/projects/niistat/), correcting for multiple comparisons using permutation tests (10,000 permutations) and a corrected alpha threshold of $p < 0.05$ for each of the four behavioral measures (Word Comprehension, Noncanonical Sentence Comprehension, Repetition, and Expressive Agrammatism). When including lesion volume as a covariate, we only identified 4 significant disconnections associated with noncanonical sentence comprehension deficits (all involving disconnection of occipital regions with either temporal pole or inferior temporal gyrus), and no significant disconnections associated with any of the other three behavioral measures we assessed (WAB-R word comprehension with PPT as a covariate; WAB-R repetition, and expressive agrammatism). It is as yet unclear whether lesion volume is critical for accurate localization as in LSM [54,55], although as noted above, lesion volume was already factored into our analyses by removing damaged tissue from estimated tractographies. Therefore, we focus our results on analyses that did not include lesion volume as a covariate in our CLSM analyses, in line with previous reports from our research group [32,42].

2.3.4. LSM and CLSM combined

The 'double disconnection' hypothesis of Mesulam et al. entails that the association between damage to temporal-parietal regions (roughly Wernicke's area) with word and sentence comprehension deficits in Wernicke's aphasia can be explained via disrupted connections from this area to the ATL and frontal cortex due to damage to underlying white matter. If this were true, then there should be no robust independent contribution of damage to these regions above and beyond the extent of disruption to these connections. To test this, we combined the LSM and CLSM data by assessing whether lesion-deficit correlations for these behavioral measures would still be statistically robust when incorporating connection strength as a covariate.

First, we identified the relevant regions associated with Word Comprehension and Noncanonical Sentence Comprehension using the ROI-based LSM analyses described in section 2.3.2. Both measures identified the same set of regions: pSTG, STG, pMTG, MTG. Then, for Word Comprehension, we identified the two most posterior of these regions (pSTG and pMTG) and identified the single strongest disconnection involving each of these regions and a more anterior temporal lobe region associated with behavioral deficits (pSTG ↔ STG, pMTG ↔ MTG pole). For Noncanonical Sentence Comprehension, we identified the single strongest disconnections involving all four of these regions identified in the ROI-based LSM analyses and a frontal lobe region. Given that no frontal-temporal disconnections were identified that survived the multiple comparisons correction in the CLSM analyses, we selected the single strongest sub-threshold frontal disconnection for these regions out of the set of IFG opercularis, IFG triangularis, IFG orbitalis, and pMFG, given that the IFG regions are classically associated with grammatical processing and the pMFG was identified in our ROI-based LSM analysis of Expressive Agrammatism. This resulted in the following four disconnections: pSTG ↔ IFG orbitalis, STG IFG ↔ opercularis, pMTG ↔ IFG orbitalis, and MTG ↔ IFG triangularis.

We then performed linear regression analyses to predict behavioral scores using proportion damage to each ROI, incorporating both lesion volume and the relevant connection for that region as covariates. In this way, we tested whether the strongest anterior temporal disconnection could account for the lesion-deficit correlations in the posterior temporal lobe for Word Comprehension, and whether the strongest frontal disconnection could account for the lesion-

deficit correlations in the temporal lobe for Noncanonical Sentence Comprehension. Under the Mesulam et al. hypothesis, we would expect that there would no longer be a significant association between the behavioral scores and damage to middle-posterior temporal lobe regions when these disconnections are considered.

2.4 Data Availability

All of the lesion maps and behavioral data for subjects enrolled in this study are available for download at https://www.dropbox.com/sh/3w4aeizgypfs7sd/AAB-W8Yn5qDUFeBj90WKsBqAa?dl=0 (use "wernickeConundrumRevisited_CLSM.xlsx" file).

3 Results

3.1 Behavioral

Non-parametric Spearman correlations found significant correlations among most of our behavioral variables when lesion volume was not included as a covariate (Table 2, top). In fact, the only correlations that were not significant were between noncanonical sentence comprehension and PPT (although this nearly survived the Bonferroni correction for multiple comparisons), and between expressive agrammatism and three measures: noncanonical sentence comprehension, WAB-R repetition, and PPT. When lesion volume was included as a covariate, we found overall weaker correlations among the behavioral measures, and expressive agrammatism was no longer significantly correlated with any of the other measures (Table 2, bottom).

Table 2 Behavioral analyses.

Analyses with no covariates					
	PNT	NonCanon	Repetition	PPT	Agramm.
Word Comp.	N = 162	N = 130	N = 218	N = 181	N = 92
	ρ = 0.565	ρ = 0.415	ρ = 0.738	ρ = 0.622	ρ = 0.377
	p < 0.001	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**
PNT		N = 102	N = 162	N = 155	N = 73
		ρ = 0.451	ρ = 0.802	ρ = 0.408	ρ = 0.350
		p < 0.001	**p < 0.001**	**p < 0.001**	**p < 0.001**
NonCanon			N = 130	N = 108	N = 79
			ρ = 0.441	ρ = 0.236	ρ = 0.101
			p < 0.001	p = 0.007	p = 0.197
Repetition				N = 181	N = 92
				ρ = 0.502	ρ = 0.205
				p < 0.001	p = 0.039
PPT					N = 75
					ρ = 0.112
					p = 0.164
Analyses with lesion volume covariate					
	PNT	NonCanon	Repetition	PPT	Agramm.

Word Comp.	N = 162	N = 130	N = 218	N = 181	N = 92
	ρ = 0.433	**ρ = 0.281**	**ρ = 0.549**	**ρ = 0.523**	ρ = 0.038
	p < 0.001	**p < 0.001**	**p < 0.001**	**p < 0.001**	p = 0.359
PNT		N = 102	N = 162	N = 155	N = 73
		ρ = 0.364	**ρ = 0.756**	**ρ = 0.306**	ρ = -0.051
		p < 0.001	**p < 0.001**	**p < 0.001**	p = 0.683
NonCanon		N = 102	N = 130	N = 108	N = 79
		ρ = 0.364	**ρ = 0.317**	ρ = 0.146	ρ = -0.137
		p < 0.001	**p < 0.001**	p = 0.067	p = 0.875
Repetition				N = 181	N = 92
				ρ = 0.359	ρ = 0.121
				p < 0.001	p = 0.152
PPT					N = 75
					ρ = -0.076
					p = 0.747

Correlation analyses that survived the Bonferroni correction for multiple comparisons within each family of tests (with/without lesion volume covariate) (adjusted alpha of $p < 0.003$) indicated in bold. ρ = Spearman's rho, Comp. = Comprehension, PNT = Philadelphia Naming Task, NonCanon = Noncanonical Sentence Comprehension, PPT = Pyramids and Palm Trees, Agramm. = Expressive Agrammatism.

Similar to Mesulam et al.[1], we found that WAB-R word comprehension and PPT scores were strongly correlated, justifying our use of PPT scores as a covariate in word comprehension to remove variance due to object recognition and non-verbal semantic processing in our lesion-symptom mapping analyses. We also found that noncanonical sentence comprehension and repetition scores were correlated, suggesting that at least some of the variance in sentence comprehension scores could be due to phonological working memory abilities.

There were notable differences from the behavioral correlations reported by [1]. Importantly, we found robust correlations between noncanonical sentence comprehension and WAB-R word comprehension, whether or not lesion volume was included as a covariate, unlike Mesulam et al., who found that these variables were not correlated. This supports the classic view in stroke-based aphasia that word and sentence comprehension deficits coincide with similar patterns of damage to Wernicke's area. We also found that WAB-R repetition was very robustly correlated with WAB-R word comprehension, whereas Mesulam et al. found that word comprehension and repetition were not correlated.

Finally, we also found that noncanonical sentence comprehension was not correlated with expressive agrammatism, whether or not lesion volume was included as a covariate. Although correlations between expressive agrammatism and other behavioral variables were not assessed in Mesulam et al.[1,12], this lack of a relationship in our data speaks against one of the major ideas promoted in this work. Namely, they suggested that sentence comprehension deficits in both PPA and stroke-based aphasia are due to degeneration and/or disconnection of a frontal-based grammatical processing center that affects both production and comprehension. Under this perspective, one would expect that both expressive agrammatism and noncanonical sentence comprehension would be correlated, but they were not. Note that we did find that expressive agrammatism correlated with WAB-R word comprehension and picture naming when lesion volume was not included as a covariate; thus the failure to identify a correlation between expressive agrammatism and noncanonical sentence comprehension cannot be merely due to a lack of statistical power.

3.2 LSM

Voxel-based LSM results are shown in Figure 1 and Supplementary Figure 1. ROI-based LSM results are listed in Table 3. Focusing on the corrected voxel-based analyses (Figure 1b), Word Comprehension (WAB-R Auditory Word Recognition deficits, with PPT scores as a covariate) deficits were associated with damage to middle and posterior STG and MTG and to a lesser extent inferior angular gyrus. Noncanonical Sentence Comprehension deficits were associated with a similar lesion distribution, although without including damage to the inferior angular gyrus. The corrected ROI analyses revealed that damage to the same set of four regions was associated with both Word Comprehension and Noncanonical Sentence Comprehension deficits: STG (middle), MTG (middle), pSTG, and pMTG. The supplementary analyses that included Repetition as a covariate for both of these measures revealed largely similar results with substantially reduced statistical strength (Supplementary Figure 1), with a subset of the same regions significantly identified in the ROI analyses (Table 3).

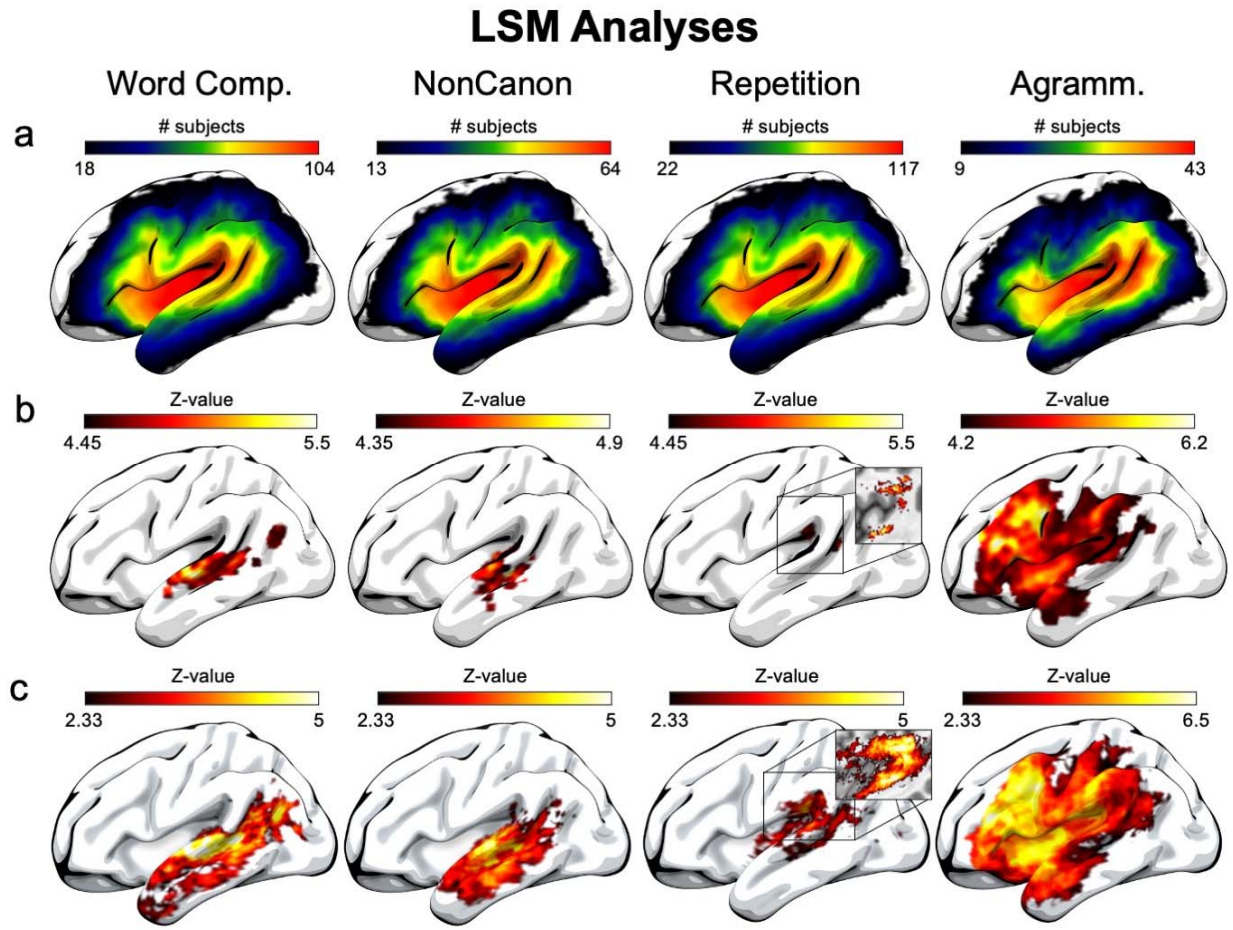

Figure 1. Lesion-symptom mapping (LSM) analyses. a) Lesion overlap maps for each group associated with the behavioral measures for which we analyzed lesion-deficit correlations. Note that the lower value in each color spectrum indicates the minimum number of subjects with damage to each region that was required for our 10% lesion load threshold. b) Voxel-wise univariate LSM analyses for each behavioral measure (incorporating lesion volume as a covariate), with a permutation correction for multiple comparisons (10,000 permutations, corrected $p < 0.05$), with results spatially smoothed for improved visibility. c) Uncorrected (voxel-wise $p < 0.01$) and unsmoothed voxel-wise univariate LSM analyses for each behavioral measure (incorporating lesion volume as a covariate). Insets show white matter damage in a medial slice of the volumetric data underlying the cortical surface not adequately depicted in the surface rendering. Comp = Comprehension, NonCanon = Noncanonical Sentence Comprehension, Agramm. = Expressive Agrammatism.

By contrast, the corrected voxel-based LSM analyses revealed that Repetition deficits were primarily associated with damage to posterior STG and superior longitudinal/arcuate fasciculus. The corrected ROI-based analyses revealed similar results, including damage to those regions as well as the posterior insula. Expressive Agrammatism was associated with a widespread pattern of damage in the corrected voxel-based analyses, including most prominently the posterior middle frontal gyrus (pMFG) and superior IFG, although this lesion map extended contiguously into the anterior insula, supramarginal gyrus, inferior angular gyrus, and ATL. The corrected ROI-based analyses of Expressive Agrammatism only revealed significant damage to the pMFG.

The voxel-based overlap analyses of Word Comprehension and Noncanonical Sentence Comprehension (Figure 2) showed substantial overlap of the lesion correlates of these two measures in the middle STG and middle-posterior STS. The centers of mass for the primary clusters of overlapping voxels were located at the following sets of MNI coordinates:

- -48, -34, -1
- -59, -16, 2
- -53, -20, -3.

This overlap is consistent with the classic picture from stroke-based aphasia in which word and sentence comprehension coincide in Wernicke's aphasia following damage to posterior temporal lobe, although we note that the strongest overlap occurred in middle STG and posterior-middle STS for both measures. Combined with the robust ROI results in both posterior and middle temporal regions, these results suggest that the middle temporal lobe is crucial to an anatomical definition of Wernicke's area. The overlap of the supplemental analyses including Repetition as a covariate showed very similar regions but with no strict overlap of Word Comprehension and Noncanonical Sentence Comprehension at the voxel level (Supplementary Figure 1), likely due to the greatly reduced statistical power of these analyses.

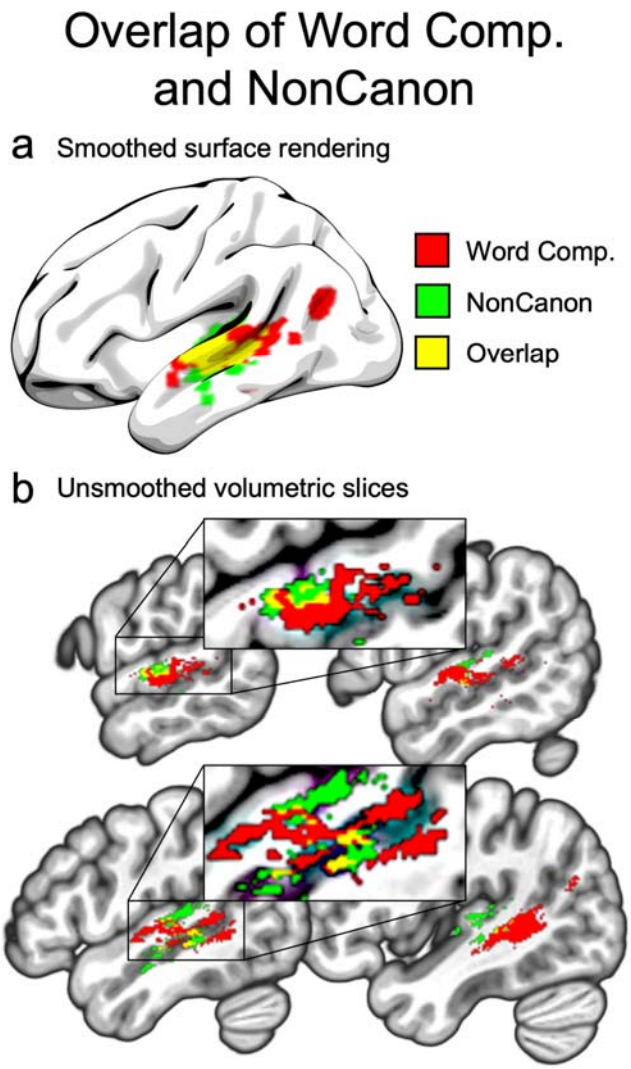

Figure 2. Overlap of the lesion maps for Word Comprehension and Noncanonical Sentence Comprehension. a) Smoothed surface rendering of the overlap (yellow) of the corrected lesion maps for Word Comprehension (red) and Noncanonical Sentence Comprehension (green). b) Unsmoothed slices of the volumetric (non-surface-rendered) overlap. Insets show zoomed-in views of the portions of the slices surrounded by rectangles. Comp = Comprehension, NonCanon = Noncanonical Sentence Comprehension.

Table 3 Significant regions from ROI-based LSM analyses.

ROI	R^2	β_u (SE)	β_s	Z	BF_m (null)
Word Comprehension					
STG	0.523	-0.009 (0.002)	-0.236	4.18	1.685e-26
MTG	0.349	-0.008 (0.002)	-0.236	3.60	8.853e-15
pSTG	0.465	-0.010 (0.002)	-0.231	3.89	3.544e-22
pMTG	0.409	-0.012 (0.002)	-0.309	4.88	2.146e-18
Noncanonical Sentence Comprehension					
STG	0.551	-0.030 (0.007)	-0.284	4.36	4.284e-20
MTG	0.410	-0.028 (0.007)	-0.305	4.10	8.183e-13
pSTG	0.491	-0.033 (0.008)	-0.282	4.08	9.572e-17
pMTG	0.388	-0.030 (0.008)	-0.282	3.75	8.102e-12
Repetition					
pSTG	0.503	-0.029 (0.007)	-0.247	4.11	1.570e-30

pInsula	0.460	-0.025 (0.007)	-0.209	3.35	9.765e-27
SLF/AF	0.634	-0.029 (0.005)	-0.300	5.70	1.319e-44
Expressive Agrammatism					
pMFG	0.510	0.768 (0.179)	0.487	4.07	3.936e-12
Word Comprehension with Repetition covariate					
pMTG	0.370	-0.009 (0.003)	-0.220	3.56	4.961e-16
Noncanonical Sentence Comprehension with Repetition covariate					
MTG	0.417	-0.031 (0.007)	-0.302	4.28	3.880e-13
STG	0.532	-0.028 (0.007)	-0.234	3.73	5.030e-19

See Figure 3 for region abbreviation definitions. All regions are left hemisphere. β_u = unstandardized estimated beta coefficient, SE = standard error, β_s = standardized estimated beta coefficient, Z = Z-score, BF_m (null) = Bayes Factor index indicating support for the null hypothesis.

3.3 CLSM

The ROIs used for CLSM analyses are shown in Figure 3. CLSM results are listed in Table 4 and shown in Figure 4. Both impaired WAB-R word comprehension (with PPT as a covariate) and noncanonical sentence comprehension were associated with several disconnections within the temporal lobe and between temporal and occipital areas. However, impaired noncanonical sentence comprehension was associated with additional disconnections between the parietal lobe (superior parietal lobule, supramarginal gyrus, postcentral gyrus) and the temporal pole, as well as two frontal-occipital disconnections (IFG pars orbitalis and lateral fronto-orbital gyrus with the Cuneus). There were no frontal-temporal or right hemisphere disconnections associated with either word or sentence comprehension deficits, and no disconnections involving Broca's area (pars triangularis and pars opercularis of IFG) or middle frontal gyrus (MFG). This speaks against the hypothesis of Mesulam et al. [1] that impaired noncanonical sentence comprehension in stroke-based aphasia results from impaired disconnection of a frontal-based grammatical processing system and that impaired word comprehension might also result from disconnection of right hemisphere temporal lobe regions.

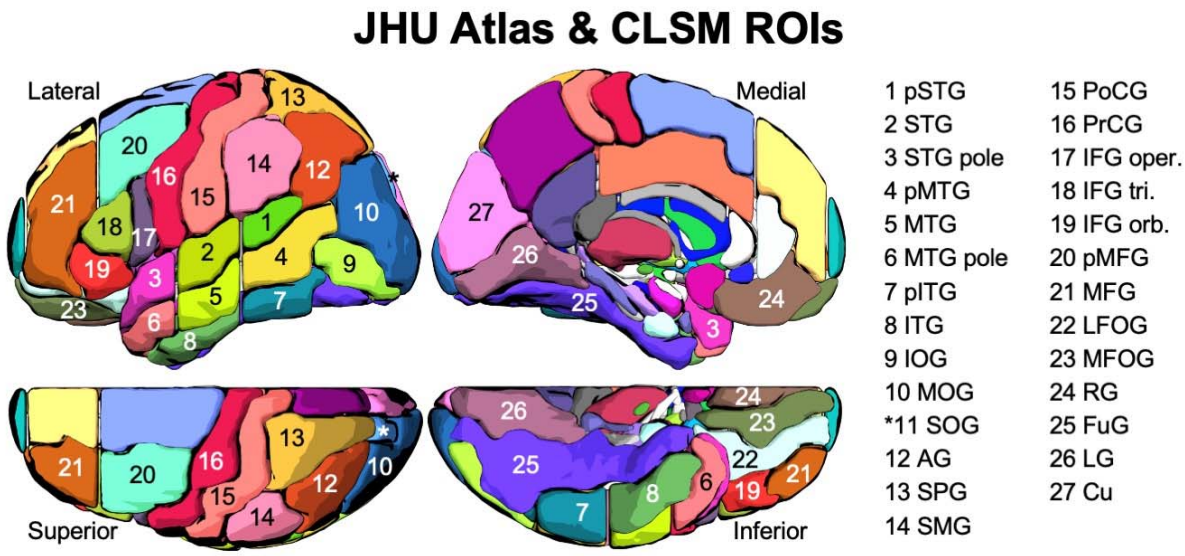

Figure 3. Illustration of the JHU atlas. Numbers correspond to the ROIs used in the CLSM analyses indicated on the right. * indicates the SOG ROI, which due to its small size and location was obscured when using a number to indicate its location. All numbered regions from the left hemisphere were included, and four corresponding right hemisphere regions were included: pSTG (1), STG (2), pMTG (4), MTG (5). AG = angular gyrus; Cu = cuneus; FuG = fusiform gyrus; IFG = inferior frontal gyrus; IOG = inferior occipital gyrus; ITG = inferior temporal gyrus;

pITG = posterior inferior temporal gyrus; LFOG = lateral fronto-orbital gyrus; LG = lingual gyrus; MOG = middle occipital gyrus; MTG = middle temporal gyrus; PoCG = postcentral gyrus; PrCG = precentral gyrus; RG = gyrus rectus; SMG = supramarginal gyrus; SOG = superior occipital gyrus; SPL = superior parietal lobule; STG = superior temporal gyrus.

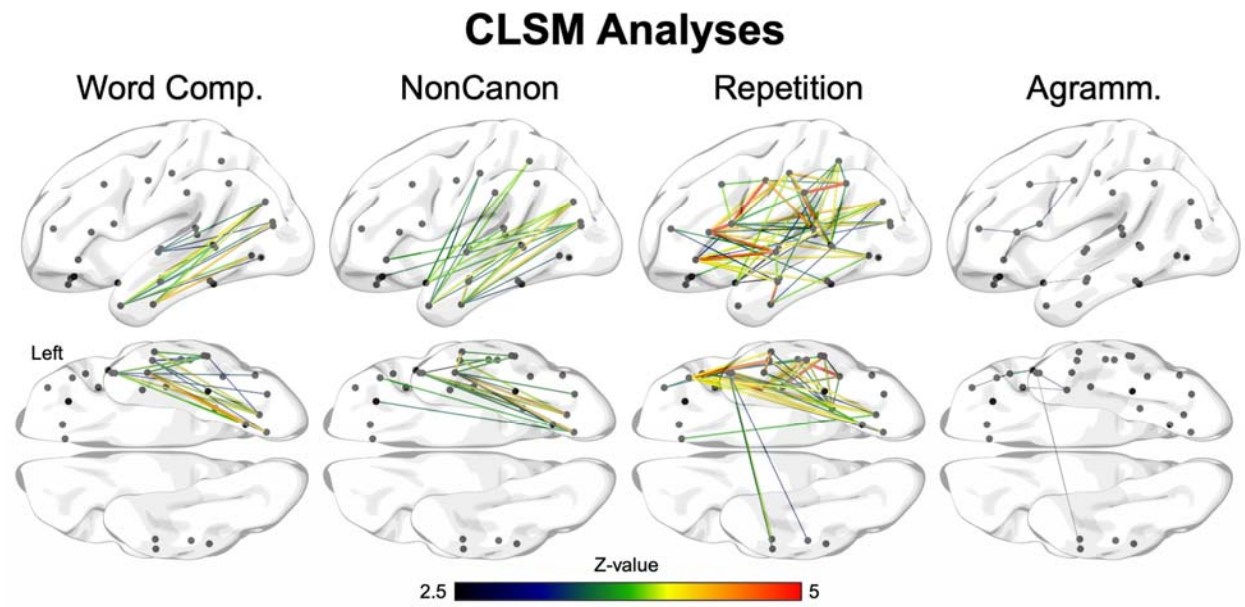

Figure 4. Connectome-based lesion-symptom mapping (CLSM) analyses. Significant connections between ROIs based on the JHU atlas[48] ascertained by diffusion tensor imaging, with a permutation correction for multiple comparisons (10,000 permutations, corrected $p < 0.05$). Dots indicate the 31 regions included in the CLSM analyses based on the JHU atlas. Comp. = Comprehension, NonCanon = Noncanonical Sentence Comprehension, Agramm. = Expressive Agrammatism.

By contrast, impaired WAB-R repetition was associated with a very large number of significant disconnections, within the frontal and temporal lobes as well as between frontal lobe and all other lobes, and between temporal lobe and all other lobes (there were no significant disconnections between parietal and occipital lobes). Expressive agrammatism was associated primarily with significant disconnections within the frontal lobe, although there was one significant frontal-temporal disconnection (between gyrus rectus and superior temporal gyrus). These results underscore that the lack of significant frontal-temporal disconnections for noncanonical sentence comprehension was not due to lack of statistical power or other methodological issues.

Table 4 Top ten significant connections in the CLSM analyses.

Connection	**R^2**	**β_u (SE)**	**β_s**	**Z**	**BF_m (null)**
Word Comprehension					
ITG ↔ LG	0.111	0.519 (0.115)	0.333	4.38	0.0007
ITG ↔ Cu	0.108	0.202 (0.045)	0.329	4.32	0.0009
MTG ↔ SOG	0.095	0.241 (0.058)	0.309	4.04	0.003
MTG pole ↔ SOG	0.093	0.068 (0.017)	0.304	3.98	0.003
ITG ↔ SOG	0.091	0.225 (0.056)	0.301	3.94	0.004
MTG pole ↔ pMTG	0.085	0.317 (0.082)	0.291	3.80	0.007
MTG pole ↔ LG	0.084	0.206 (0.053)	0.290	3.79	0.007
ITG ↔ pMTG	0.081	0.692 (0.182)	0.285	3.72	0.009
MTG ↔ pMTG	0.081	0.743 (0.196)	0.284	3.71	0.009
MTG pole ↔ Cu	0.073	0.077 (0.022)	0.271	3.53	0.017
Noncanonical Sentence Comprehension					

ITG ↔ Cu	0.141	0.604 (0.134)	0.375	4.33	0.0008
ITG ↔ SOG	0.140	0.785 (0.175)	0.374	4.31	0.0009
MTG ↔ ITG	0.126	0.760 (0.180)	0.355	4.08	0.002
MTG pole ↔ SOG	0.118	0.207 (0.051)	0.343	3.93	0.004
STG ↔ SOG	0.116	1.082 (0.268)	0.341	3.91	0.004
STG pole ↔ SOG	0.115	0.214 (0.053)	0.339	3.88	0.005
SPL ↔ STG pole	0.114	0.064 (0.016)	0.338	3.87	0.005
SPL ↔ MTG pole	0.112	0.083 (0.021)	0.334	3.82	0.006
STG ↔ pSTG	0.108	1.533 (0.396)	0.328	3.75	0.008
ITG ↔ pMTG	0.106	2.262 (0.590)	0.326	3.72	0.008
Repetition					
IFG opercularis ↔ IFG triangularis	0.119	1.296 (0.252)	0.345	4.97	0.00005
IFG opercularis ↔ PrCG	0.117	0.742 (0.146)	0.342	4.94	0.00006
SMG ↔ AG	0.115	1.278 (0.253)	0.339	4.89	0.00007
IFG orbitalis ↔ STG	0.107	0.367 (0.076)	0.327	4.71	0.0002
PoCG ↔ PMTG	0.107	0.419 (0.086)	0.328	4.71	0.0002
IFG triangularis ↔ STG	0.106	0.184 (0.038)	0.326	4.68	0.0002
MTG ↔ ITG	0.102	0.662 (0.141)	0.319	4.58	0.0003
PrCG ↔ PSTG	0.098	0.363 (0.078)	0.314	4.50	0.0004
IFG triangularis ↔ PoCG	0.095	0.192 (0.042)	0.309	4.42	0.0006
PoCG ↔ AG	0.092	0.758 (0.170)	0.304	4.35	0.0008
Expressive Agrammatism					
IFG opercularis ↔ IFG triangularis	0.135	-0.011 (0.003)	-0.368	3.57	0.014
IFG opercularis ↔ PrCG	0.091	-0.014 (0.005)	-0.302	2.89	0.105
MFG ↔ IFG triangularis	0.086	-0.024 (0.008)	-0.294	2.81	0.128
IFG orbitalis ↔ IFG triangularis	0.080	-0.010 (0.004)	-0.284	2.71	0.166
pMFG ↔ PrCG	0.080	-0.007 (0.002)	-0.282	2.69	0.172
STG pole ↔ MTG (RH)	0.074	-1.574 (0.594)	-0.272	2.59	0.221

See Figure 3 for region abbreviation definitions. All regions are left hemisphere, unless indicated as right hemisphere with (RH).
β_u = unstandardized estimated beta coefficient, SE = standard error, β_s = standardized estimated beta coefficient, Z = Z-score, BF_m (null) = Bayes Factor index indicating support for the null hypothesis.

3.4 LSM and CLSM combined

Examining the full list of significant CLSM results in Supplementary Table 3 shows that the strongest disconnection for Word Comprehension involving the pSTG was with the STG, and the strongest disconnection involving the pMTG was with the MTG pole. Given that there were no significant frontal-temporal disconnections for Noncanonical Sentence Comprehension that survived the multiple comparisons correction, we examined the sub-threshold connections between the four temporal lobe regions associated with this behavioral measure and four frontal regions: each of the three IFG subregions (classically associated with grammatical processing) and the pMFG (identified in our LSM analysis of Expressive Agrammatism) (Supplementary Table 1. This resulted in the following strongest relevant frontal-temporal disconnections: pSTG ↔ IFG orbitalis, STG IFG ↔ opercularis, pMTG ↔ IFG orbitalis, and MTG ↔ IFG triangularis.

Supplementary Table 2 shows the results of the combined analyses. The lesion-deficit correlations for pSTG and pMTG for Word Comprehension remained statistically robust even when including the strongest relevant posterior-anterior disconnections, and the lesion-deficit correlations for pSTG, STG, pMTG, and MTG for Noncanonical Sentence Comprehension also remained statistically robust even when including the strongest relevant temporal-frontal disconnections. Thus, there remains a strong independent association between damage to middle-

posterior temporal lobe regions and comprehension deficits even when accounting for their relevant disconnections to ATL and the frontal lobe.

4 Discussion

Consistent with previous research, the lesion correlates of Word Comprehension (with PPT as a covariate) and Noncanonical Sentence Comprehension deficits in chronic post-stroke aphasia converged on the middle-posterior temporal lobe in our lesion symptom mapping (LSM) analyses, overlapping in the middle STG and middle-posterior STS. The supplementary analyses of these measures including Repetition as a covariate resulted in similar lesion maps but with greatly reduced statistical power, without significant overlap but in nearly identical locations. This is roughly consistent with the historical definition of Wernicke's area as the posterior temporal lobe, although it should be noted that robust overlap occurred more anteriorly than as often depicted. In general, we agree with others who have argued[3,58] that the term "Wernicke's area" should be avoided because of potential confusion about its localization stemming the scattered historical anatomical localization of Wernicke's area that most often focuses on more posterior temporal-parietal regions[1,2]. However, our results do reinforce the mostly uncontroversial conclusion that the temporal lobe regions associated with both word and sentence comprehension deficits in stroke-based aphasia are clearly posterior to the anterior locus of word comprehension deficits identified in the papers reported by Mesulam et al.[1,12]

One of the main claims of Mesulam et al.[1] is that damage to the territory associated with Wernicke's area involves "double disconnection" in Wernicke's aphasia. That is, they posited that word comprehension deficits follow from disconnection between superior temporal cortex (either left or right hemisphere) and the anterior temporal lobe (ATL), and sentence comprehension deficits follow from disconnection between superior temporal cortex and frontal cortex. However, while our connectome-based lesion-symptom mapping (CLSM) analyses found that there were significant disconnections involving the temporal pole for both word and noncanonical sentence comprehension deficits, there were no frontal-temporal, frontal-parietal, or right temporal lobe disconnections involved in either. In our exploratory analyses, we did find that there were some sub-threshold frontal-temporal disconnections associated with noncanonical sentence comprehension that approached significance. However, our combined LSM and CLSM analyses further showed that, using the strongest sub-threshold frontal-temporal connections as a covariate, there were still robust effects of damage to middle and posterior temporal lobe regions. There was also no significant behavioral correlation between noncanonical sentence comprehension and expressive agrammatism, while there was a significant behavioral correlation between noncanonical sentence comprehension and word comprehension. Thus, the fundamental prediction of Mesulam et al. that sentence comprehension deficits associated with damage to Wernicke's area are explained by a frontal disconnection pattern, and that word and sentence comprehension deficits dissociate, was disconfirmed. Note that our results are unlikely to be due to lack of statistical power, as we identified significant frontal-temporal disconnections associated with speech repetition deficits, and a significant VLSM effect of expressive agrammatism in frontal areas (particularly posterior MFG) as well as somewhat weaker effects in the ATL, with significantly damaged connections involving IFG and adjacent frontal regions.

The Mesulam et al. frontal-temporal disconnection proposal regarding sentence comprehension deficits has logical force if a primary cortical locus of syntactic comprehension were in the frontal lobe, as suggested by many authors [59–63]. Accordingly, we did find that agrammatic production deficits are associated with damage to the frontal lobe, including Broca's area/posterior IFG, consistent with previous work [30,42,43,64–68]. In addition, functional neuroimaging studies of syntactic processing do reliably identify frontal activations including Broca's area as indicated by meta-analyses of these studies[69,70]. However, recent theories propose that the systems for building hierarchical syntactic structure in *comprehension* are in the posterior temporal lobe, and not the frontal lobe[16,65]. The lack of a significant association between noncanonical sentence comprehension deficits and damage to the inferior or middle frontal lobe, and the lack of an association with significant frontal-temporal disconnections, provides evidence against the view that syntactic computations associated with sentence comprehension are processed in or around Broca's area and instead support the hypothesis that syntactic comprehension critically recruits posterior temporal cortex instead. Matchin and Hickok (2020) also proposed that the neural correlates for hierarchical syntax and lexical access are in the same region, intimately intertwined, which is consistent with modern approaches to syntax positing "lexicalized" syntactic representations. Under this view, coincidence of the lesion correlates of lexical and syntactic processing in the posterior temporal lobe is expected. However, we must also keep in mind that the lack of frontal effects for syntactic comprehension might also be due to functional reorganization in chronic aphasia, and there is some evidence that people with chronic aphasia show enhanced activity for language processing in right IFG relative to healthy controls, as revealed by a recent meta-analysis[72].

Importantly, our analyses of noncanonical sentence comprehension were matched to Mesulam et al.[1] in assessing *overall* comprehension ability. Previous studies from our group in stroke-based aphasia that have examined *residual* performance on noncanonical structures after controlling for performance to canonical structures have associated deficits with damage to frontal regions [28,73] (with other studies showing conflicting results[23,42,43]. Residual performance on noncanonical sentence comprehension after controlling for canonical sentence comprehension likely strongly highlights executive function resources that are necessary for processing particularly complex structures and revising sentence interpretation [74–80], thus some implication of frontal regions that are associated with these supporting mechanisms is expected [19,81–84]. The sub-threshold disconnections we identified in our exploratory analyses provide some support for this account.

One prediction of Mesulam et al.[1] was partially confirmed: word comprehension deficits involved disconnection of anterior temporal regions. The disconnections we found, between anterior temporal regions and other temporal lobe regions and visual cortex, were not unique to word comprehension deficits, as similar disconnections were associated with noncanonical sentence comprehension deficits. However, we take the primary claim of Mesulam et al. to be not that disconnections of ATL are associated with word comprehension impairments, but rather that these disconnections *explain* the association of posterior temporal lobe damage with these impairments. Critically, our combined LSM/CLSM analyses revealed that damage to pSTG and pMTG was robustly associated with word comprehension impairments even when including the strongest disconnections between these regions and more anterior temporal lobe regions (STG and MTG pole, respectively). In addition, we also tested the possibility raised by Mesulam et al.

that word comprehension impairments are associated with disconnection of right hemisphere regions, but no significant disconnections were identified.

The Mesulam et al. hypothesis would also predict that damage to the ATL itself should be associated with word comprehension deficits. However, we note that the corrected voxel-based LSM analyses of Word Comprehension (when controlling for conceptual-semantic processing via the PPT covariate) did not reveal an association with ATL damage. This lack of a robust ATL effect for Word Comprehension is unlikely to be due to statistical power, as we had adequate lesion coverage in this area and did identify significant effects for Expressive Agrammatism there. Overall, these combined results speak against the disconnection hypothesis of Mesulam et al. They suggest that the ATL may play a supporting role for word comprehension by retrieving conceptual-semantic representations which are necessary to perform a picture task in some contexts, and thus ATL disconnection contributes in a minor way to the impaired word comprehension performance seen in many patients with post-stroke aphasia involving damage to the posterior temporal lobe.

Under Mesulam et al.'s hypothesis, Wernicke's area (broadly construed) plays a key role in phonological short-term/working memory, which is in line with their reported association between repetition deficits and posterior temporal cortical degeneration [12]. Consistent with this, in our study, repetition deficits were associated with arcuate fasciculus and posterior temporal damage and multiple frontal-parietal-temporal disconnections. Furthermore, deficits in noncanonical sentence comprehension (but not auditory word comprehension), were associated with significant disconnections of the parietal and temporal lobe. This converges with previous reports of associations between deficits in complex sentence comprehension and inferior parietal lobe damage in chronic stroke patients with aphasia [20,21,23,24,29,42,73,85], as well as functional neuroimaging studies finding activation for sensory-motor integration in this vicinity[35,37,86]. It is possible that these disconnections reflect the additional phonological short term memory resources that are useful in parsing sentence structure that are not typically required for word comprehension [75–78,87–89,89], which may explain why the significant correlation between word and sentence comprehension abilities was only moderate in strength. There were two frontal disconnections associated with deficits in noncanonical sentence comprehension (IFG orbitalis and lateral frontal-orbital gyrus), but neither of these regions are traditionally associated with grammatical processing, and both involved a disconnection with the cuneus (a part of early visual cortex) and not the temporal lobe.

Under our account, in which the middle-posterior temporal lobe plays a dominant causal role in both lexical access and syntactic comprehension, one would expect a strong association between word and sentence comprehension deficits and degeneration of the middle and posterior temporal lobe in PPA. However, this is not what is seen, as patients with the logopenic variant of PPA and posterior temporal-parietal degeneration do not typically show notable word comprehension deficits[1,90–92] (but see Bonner & Grossman[93]). Also, Mesulam et al.[1] do not report a notable association of atrophy in middle-posterior temporal lobe with deficits in noncanonical sentence comprehension. Why not? Some of the present authors have previously suggested that logopenic PPA does not necessarily involve complete degeneration of posterior temporal-parietal cortex, and that remaining neurons may be sufficient to perform the basic phonological and lexical access functions [8]. Additionally, some models posit an important role for the right hemisphere in

phonological processing and lexical access [94–96], which could sufficiently compensate for left hemisphere degeneration. This is consistent with recent demonstrations of small but significant word comprehension deficits in right hemisphere stroke [97].

One area of agreement between Mesulam et al. and our data is that damage or degeneration of the ATL is not implicated in noncanonical sentence comprehension deficits. However, we did find significant disconnections of the temporal pole ROIs related to impaired noncanonical sentence comprehension deficits. This is consistent with previous reports implicating damage to anterior temporal lobe in grammatical processing deficits [20,29]. Nevertheless, we suggest that the (relatively less common) implication of ATL damage or disconnection in sentence comprehension deficits likely reflects semantic rather than syntactic deficits [19,58], which is consistent with functional neuroimaging data [98–102].

Why is there such a strong correlation between word comprehension deficits and peak ATL atrophy in PPA? For one, PPA is a progressive neurodegenerative disease which evolves to ultimately affect a number of cognitive domains [103,104], and functional neuroimaging studies of people with the semantic variant of PPA have shown abnormal activation patterns and functional connectivity in regions outside the ATL [105–111]. This suggests that the neuropathology of semantic PPA is more widespread than what shows up in gross measures of grey matter atrophy and may affect a broader network (potentially including middle and posterior temporal cortex) that contributes to word comprehension impairments. Individuals with PPA show neural degeneration far beyond the areas of peak atrophy (as seen in the figures in Mesulam et al.[1]), as well as disrupted functional networks beyond the sites of major neural degeneration. Longitudinal MRI and word comprehension testing reveals that deterioration in auditory word comprehension over time in PPA is associated with within-individual atrophy over time in left middle temporal cortex, left angular gyrus, and right inferior and middle temporal cortex [112]. Second, the word level comprehension deficits seen in stroke patients and svPPA might be qualitatively different. Word comprehension deficits in stroke may be much more commonly due to deficits in basic linguistic processing, i.e. at the phonological processing and lexical/lemma access levels, whereas word comprehension deficits in PPA may be largely due to deficits in accessing fine-grained semantic features of words downstream from lexical access. These semantic features could be characteristics of word representations rather than amodal conceptual information, which may remain intact in svPPA [113]. These may be more completely disrupted in semantic PPA due to the pattern of neurodegeneration than is seen with strokes impinging on this area, or in resections.

Additionally, it is worth noting that the word comprehension task used by Mesulam et al. consists of moderately difficult items of the Peabody Picture Vocabulary Task (PPVT) [114], which involve much more complex semantic inference than the task we used, the Auditory Word Comprehension subtest of the WAB-R [39]. We prefer the WAB-R word comprehension test as a basic measure of phonological and lexical processing, as it limits semantic processing demands as well as not requiring fine-grained visual processing and object recognition by asking subjects to pick out real world objects on most trials. Future studies should examine the relationship between these word comprehension measures and the results obtained in lesion-symptom mapping analyses in both PPA and stroke-based aphasia.

Overall, our combined VLSM and CLSM results speak against the hypothesis of Mesulam et al. (2015) of a double disconnection syndrome underlying word and sentence/syntactic comprehension deficits in post-stroke aphasia. Rather, our results support the classical concept of Wernicke's area as directly supporting both word and sentence comprehension, although our results do suggest that anterior temporal lobe and inferior parietal networks bolster core linguistic processing through semantic and phonological working memory resources, respectively. The discrepancy between our results and those of Mesulam et al. from PPA might be explained by differences between language deficits in post-stroke aphasia versus PPA or differences in tests used to assess comprehension, as described above. Alternatively, the conclusions based on PPA might be unfounded, because they were based on regions of peak atrophy associated with errors, rather than considering other areas of degeneration or dysfunction that might be responsible for deficits. Irrespective of the account of the discrepant results, our data provide strong evidence for the major role of Wernicke's area in both word and sentence comprehension.

Acknowledgments

We would also like to thank Alexandra Basilakos and Brielle C. Stark for assistant with rating of speech samples, Leigh Ann Spell, Allison Croxton, Anna Doyle, Michele Martin, Katie Murphy, and Sara Sayers for their assistance with data collection, and graduate student clinicians in the Aphasia Lab for transcribing and coding speech samples. Finally, we would like to thank two anonymous reviewers for their fruitful analysis suggestions.

Funding

This research was supported by National Institute on Deafness and Other Communication Disorders grants P50 DC014664 and U01 DC011739 awarded to Julius Fridriksson, and grant R01 DC014021 awarded to Leonardo Bonilha.

Competing interests

The authors report no competing interests.

References

1. Mesulam MM, Thompson CK, Weintraub S, Rogalski EJ. The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. *Brain*. 2015;138(8):2423-2437. doi:10.1093/brain/awv154

2. Bogen JE, Bogen GM. Wernicke's region - where is it? *Ann N Y Acad Sci*. 1976;280(1 Origins and E):834-843. doi:10.1111/j.1749-6632.1976.tb25546.x

3. Tremblay P, Dick AS. Broca and Wernicke are dead, or moving past the classic model of language neurobiology. *Brain Lang*. 2016;162:60-71. doi:10.1016/j.bandl.2016.08.004

4. Geschwind N. Language and the Brain. *Sci Am*. 1972;226(4):76-83.

5. Geschwind N. Specializations of the Human Brain. *Sci Am*. 1979;241(3):180-199. doi:10.1038/scientificamerican0979-180

6. Lichtheim L. On aphasia. *Brain*. 1885;7:433-484.

7. Wernicke C. The symptom complex of aphasia: A psychological study on an anatomical basis. In: Cohen RS, Wartofsky MW, eds. *Boston Studies in the Philosophy of Science*. D. Reidel Publishing Company; 1874:34-97.

8. Hillis AE, Rorden C, Fridriksson J. Brain regions essential for word comprehension: Drawing inferences from patients: Lesion-Deficit Mapping. *Ann Neurol*. 2017;81(6):759-768. doi:10.1002/ana.24941

9. Damasio AR. Aphasia. *N Engl J Med*. 1992;326(8):531-539.

10. Hillis AE. Aphasia: Progress in the last quarter of a century. *Neurology*. 2007;69(2):200-213. doi:10.1212/01.wnl.0000265600.69385.6f

11. Howard D, Patterson K. *The Pyramids and Palm Trees Test: A Test of Semantic Access from Words and Pictures*. Harcourt Assessment; 1992.

12. Mesulam MM, Rader BM, Sridhar J, et al. Word comprehension in temporal cortex and Wernicke area: A PPA perspective. *Neurology*. 2019;92(3):e224-e233. doi:10.1212/WNL.0000000000006788

13. Bonilha L, Rorden C, Fridriksson J. Assessing the Clinical Effect of Residual Cortical Disconnection After Ischemic Strokes. *Stroke*. 2014;45(4):988-993. doi:10.1161/STROKEAHA.113.004137

14. Fridriksson J, Bonilha L, Rorden C. Severe Broca's Aphasia without Broca's Area Damage. *Behav Neurol*. 2007;18(4):237-238. doi:10.1155/2007/785280

15. Catani M, Mesulam M. The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex*. 2008;44(8):953-961. doi:10.1016/j.cortex.2008.04.002

16. Hagoort P, Indefrey P. The Neurobiology of Language Beyond Single Words. *Annu Rev Neurosci*. 2014;37(1):347-362. doi:10.1146/annurev-neuro-071013-013847

17. Lau EF, Phillips C, Poeppel D. A cortical network for semantics: (de)constructing the N400. *Nat Rev Neurosci*. 2008;9(12):920-933. doi:10.1038/nrn2532

18. Fedorenko E, Blank IA, Siegelman M, Mineroff Z. Lack of selectivity for syntax relative to word meanings throughout the language network. *Cognition*. 2020;203:104348. doi:10.1016/j.cognition.2020.104348

19. Matchin W, Hickok G. The Cortical Organization of Syntax. *Cereb Cortex*. 2020;30(3):1481-1498.

20. Dronkers NF, Wilkins DP, Van Valin RD, Redfern BB, Jaeger JJ. Lesion analysis of the brain areas involved in language comprehension. *Cognition*. 2004;92(1-2):145-177. doi:10.1016/j.cognition.2003.11.002

21. Pillay SB, Binder JR, Humphries C, Gross WL, Book DS. Lesion localization of speech comprehension deficits in chronic aphasia. *Neurology*. 2017;88(10):970-975. doi:10.1212/WNL.0000000000003683

22. Race DS, Ochfeld E, Leigh R, Hillis AE. Lesion analysis of cortical regions associated with the comprehension of Nonreversible and Reversible yes/no questions. *Neuropsychologia*. 2012;50(8):1946-1953. doi:10.1016/j.neuropsychologia.2012.04.019

23. Rogalsky C, LaCroix AN, Chen KH, et al. The Neurobiology of Agrammatic Sentence Comprehension: A Lesion Study. *J Cogn Neurosci*. 2018;30(2):234-255. doi:10.1162/jocn_a_01200

24. Thothathiri M, Kimberg DY, Schwartz MF. The Neural Basis of Reversible Sentence Comprehension: Evidence from Voxel-based Lesion Symptom Mapping in Aphasia. *J Cogn Neurosci*. 2012;24(1):212-222. doi:10.1162/jocn_a_00118

25. Wilson SM, Saygın AP. Grammaticality Judgment in Aphasia: Deficits Are Not Specific to Syntactic Structures, Aphasic Syndromes, or Lesion Sites. *J Cogn Neurosci*. 2004;16(2):238-252. doi:10.1162/089892904322984535

26. Den Ouden DB, Saur D, Mader W, et al. Network modulation during complex syntactic processing. *NeuroImage*. 2012;59(1):815-823. doi:10.1016/j.neuroimage.2011.07.057

27. Amici S, Brambati SM, Wilkins DP, et al. Anatomical Correlates of Sentence Comprehension and Verbal Working Memory in Neurodegenerative Disease. *J Neurosci*. 2007;27(23):6282-6290. doi:10.1523/JNEUROSCI.1331-07.2007

28. Fridriksson J, den Ouden DB, Hillis AE, et al. Anatomy of aphasia revisited. *Brain*. 2018;141(3):848-862. doi:10.1093/brain/awx363

29. Magnusdottir S, Fillmore P, den Ouden DB, et al. Damage to left anterior temporal cortex predicts impairment of complex syntactic processing: A lesion-symptom mapping study: ATL Damage Impairs Complex Syntax Processing. *Hum Brain Mapp*. 2013;34(10):2715-2723. doi:10.1002/hbm.22096

30. Wilson SM, Galantucci S, Tartaglia MC, et al. Syntactic Processing Depends on Dorsal Language Tracts. *Neuron*. 2011;72(2):397-403. doi:10.1016/j.neuron.2011.09.014

31. Baldo JV, Dronkers NF. Neural correlates of arithmetic and language comprehension: A common substrate? *Neuropsychologia*. 2007;45(2):229-235. doi:10.1016/j.neuropsychologia.2006.07.014

32. Bonilha L, Hillis AE, Hickok G, den Ouden DB, Rorden C, Fridriksson J. Temporal lobe networks supporting the comprehension of spoken words. *Brain*. 2017;140(9):2370-2380. doi:10.1093/brain/awx169

33. Del Gaizo J, Fridriksson J, Yourganov G, et al. Mapping Language Networks Using the Structural and Dynamic Brain Connectomes. *eneuro*. 2017;4(5):ENEURO.0204-17.2017. doi:10.1523/ENEURO.0204-17.2017

34. Yourganov G, Fridriksson J, Rorden C, Gleichgerrcht E, Bonilha L. Multivariate Connectome-Based Symptom Mapping in Post-Stroke Patients: Networks Supporting Language and Speech. *J Neurosci*. 2016;36(25):6668-6679. doi:10.1523/JNEUROSCI.4396-15.2016

35. Buchsbaum BR, Baldo J, Okada K, et al. Conduction aphasia, sensory-motor integration, and phonological short-term memory – An aggregate analysis of lesion and fMRI data. *Brain Lang*. 2011;119(3):119-128. doi:10.1016/j.bandl.2010.12.001

36. Buchsbaum BR, D'Esposito M. A sensorimotor view of verbal working memory. *Cortex*. 2019;112:134-148. doi:10.1016/j.cortex.2018.11.010

37. Hickok G, Buchsbaum B, Humphries C, Muftuler T. Auditory–Motor Interaction Revealed by fMRI: Speech, Music, and Working Memory in Area Spt. *J Cogn Neurosci*. 2003;15(5):10.

38. Ravizza SM, Delgado MR, Chein JM, Becker JT, Fiez JA. Functional dissociations within the inferior parietal cortex in verbal working memory. *NeuroImage*. 2004;22(2):562-573. doi:10.1016/j.neuroimage.2004.01.039

39. Kertesz A. *Western Aphasia Battery- Revised*. Grune and Stratton; 2007.

40. Cho-Reyes S, Thompson CK. Verb and sentence production and comprehension in aphasia: Northwestern Assessment of Verbs and Sentences (NAVS). *Aphasiology*. 2012;26(10):1250-1277. doi:10.1080/02687038.2012.693584

41. Magnusdottir S. *Setningafræðipróf (Test of Syntax)*. Landspítali University Hospital; 2005.

42. Den Ouden D, Malyutina S, Basilakos A, et al. Cortical and structural connectivity damage correlated with impaired syntactic processing in aphasia. *Hum Brain Mapp*. 2019;40(7):2153-2173. doi:10.1002/hbm.24514

43. Matchin W, Basilakos A, Stark BC, den Ouden DB, Fridriksson J, Hickok G. Agrammatism and paragrammatism: a cortical double dissociation revealed by lesion-symptom mapping. *Neurobiol Lang*. Published online April 14, 2020:1-47. doi:10.1162/nol_a_00010

44. Roach A, Schwartz MF, Martin N, Grewal RS, Brecher A. The Philadelphia Naming Test: Scoring and rationale. *Clin Aphasiology*. 1996;24:121-133.

45. Goodglass H, Kaplan E. *Boston Diagnostic Aphasia Examination (BDAE)*. 2nd ed. Lippincott Williams & Wilkins; 1983.

46. MacWhinney B, Fromm D, Forbes M, Holland A. AphasiaBank: Methods for studying discourse. *Aphasiology*. 2011;25(11):1286-1307. doi:10.1080/02687038.2011.589893

47. Ashburner J, Friston KJ. Unified segmentation. *NeuroImage*. 2005;26(3):839-851. doi:10.1016/j.neuroimage.2005.02.018

48. Faria AV, Joel SE, Zhang Y, et al. Atlas-based analysis of resting-state functional connectivity: Evaluation for reproducibility and multi-modal anatomy–function correlation studies. *NeuroImage*. 2012;61(3):613-621. doi:10.1016/j.neuroimage.2012.03.078

49. Joliot M, Jobard G, Naveau M, et al. AICHA: An atlas of intrinsic connectivity of homotopic areas. *J Neurosci Methods*. 2015;254:46-59. doi:10.1016/j.jneumeth.2015.07.013

50. JASP Team. *JASP*.; 2020.

51. Basso A, Capitani E, Laiacona M, Luzzatti C. Factors Influencing Type and Severity of Aphasia. *Cortex*. 1980;16(4):631-636. doi:10.1016/S0010-9452(80)80011-6

52. Kertesz A, Harlock W, Coates R. Computer tomographic localization, lesion size, and prognosis in aphasia and nonverbal impairment. *Brain Lang*. 1979;8(1):34-50. doi:10.1016/0093-934X(79)90038-5

53. Lahiri D, Dubey S, Ardila A, Ray BK. Factors affecting vascular aphasia severity. *Aphasiology*. 2021;35(5):633-641. doi:10.1080/02687038.2020.1712587

54. DeMarco AT, Turkeltaub PE. A multivariate lesion symptom mapping toolbox and examination of lesion volume biases and correction methods in lesion symptom mapping. *Hum Brain Mapp*. 2018;39(11):4169-4182. doi:10.1002/hbm.24289

55. Ivanova MV, Herron TJ, Dronkers NF, Baldo JV. An empirical comparison of univariate versus multivariate methods for the analysis of brain–behavior mapping. *Hum Brain Mapp*. 2021;42:1070-1101.

56. Baldo JV, Wilson SM, Dronkers NF. Uncovering the Neural Substrates of Language: A Voxel-Based Lesion-Symptom Mapping Approach. In: Faust M, ed. *The Handbook of the Neuropsychology of Language*. Wiley-Blackwell; 2012:582-594. doi:10.1002/9781118432501.ch28

57. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*. 2007;34(1):144-155. doi:10.1016/j.neuroimage.2006.09.018

58. Binder JR. Current Controversies on Wernicke's Area and its Role in Language. *Curr Neurol Neurosci Rep*. 2017;17(8):58. doi:10.1007/s11910-017-0764-8

59. Friederici AD. *Language in Our Brain: The Origins of a Uniquely Human Capacity*. MIT Press; 2017.

60. Grodzinsky Y, Pieperhoff P, Thompson C. Stable brain loci for the processing of complex syntax: A review of the current neuroimaging evidence. *Cortex*. 2021;142:252-271. doi:10.1016/j.cortex.2021.06.003

61. Hagoort P. The neurobiology of language beyond single-word processing. *Science*. 2019;366(6461):55-58. doi:10.1126/science.aax0289

62. Tyler LK, Marslen-Wilson W. Fronto-temporal brain systems supporting spoken language comprehension. *Philos Trans R Soc B Biol Sci*. 2008;363(1493):1037-1054. doi:10.1098/rstb.2007.2158

63. Ullman MT. The Declarative/Procedural Model. In: *Neurobiology of Language*. Elsevier; 2016:953-968. doi:10.1016/B978-0-12-407794-2.00076-6

64. Fridriksson J, Fillmore P, Guo D, Rorden C. Chronic Broca's Aphasia Is Caused by Damage to Broca's and Wernicke's Areas. *Cereb Cortex*. 2015;25(12):4689-4696. doi:10.1093/cercor/bhu152

65. Mesulam MM. Primary progressive aphasia and the language network: The 2013 H. Houston Merritt Lecture. *Neurology*. 2013;81(5):456-462. doi:10.1212/WNL.0b013e31829d87df

66. Sapolsky D, Bakkour A, Negreira A, et al. Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology*. 2010;75(4):358-366. doi:10.1212/WNL.0b013e3181ea15e8

67. Wilson SM, Dronkers NF, Ogar JM, et al. Neural Correlates of Syntactic Processing in the Nonfluent Variant of Primary Progressive Aphasia. *J Neurosci*. 2010;30(50):16845-16854. doi:10.1523/JNEUROSCI.2547-10.2010

68. Wilson SM, Henry ML, Besbris M, et al. Connected speech production in three variants of primary progressive aphasia. *Brain*. 2010;133(7):2069-2088. doi:10.1093/brain/awq129

69. Zaccarella E, Schell M, Friederici AD. Reviewing the functional basis of the syntactic Merge mechanism for language: A coordinate-based activation likelihood estimation meta-analysis. *Neurosci Biobehav Rev*. 2017;80:646-656. doi:10.1016/j.neubiorev.2017.06.011

70. Meyer L, Friederici AD. Neural Systems Underlying the Processing of Complex Sentences. In: Hickok G, Small SL, eds. *Neurobiology of Language*. Elsevier; 2016:597-606. doi:10.1016/B978-0-12-407794-2.00048-1

71. Bornkessel-Schlesewsky I, Schlesewsky M. Reconciling time, space and function: A new dorsal–ventral stream model of sentence comprehension. *Brain Lang*. 2013;125(1):60-76. doi:10.1016/j.bandl.2013.01.010

72. Wilson SM, Schneck SM. Neuroplasticity in Post-Stroke Aphasia: A Systematic Review and Meta-Analysis of Functional Imaging Studies of Reorganization of Language Processing. *Neurobiol Lang*. 2020;2(1):22-82. doi:10.1162/nol_a_00025

73. Kristinsson S, Thors H, Yourganov G, et al. Brain Damage Associated with Impaired Sentence Processing in Acute Aphasia. *J Cogn Neurosci*. 2020;32(2):256-271. doi:10.1162/jocn_a_01478

74. Caplan D, Waters G. Memory mechanisms supporting syntactic comprehension. *Psychon Bull Rev*. 2013;20(2):243-268. doi:10.3758/s13423-012-0369-9

75. Gibson E. Linguistic complexity: locality of syntactic dependencies. *Cognition*. 1998;68(1):1-76. doi:10.1016/S0010-0277(98)00034-1

76. Just MA, Carpenter PA. A capacity theory of comprehension: Individual differences in working memory. *Psychol Rev*. 1992;99(1):122-149.

77. Lewis RL, Vasishth S, Van Dyke JA. Computational principles of working memory in sentence comprehension. *Trends Cogn Sci*. 2006;10(10):447-454. doi:10.1016/j.tics.2006.08.007

78. Miller GA, Chomsky N. Finitary Models of Language Users. In: *Handbook of Mathematical Psychology*. Vol 2. Wiley; 1963:419-491.

79. Novick JM, Trueswell JC, Thompson-Schill SL. Cognitive control and parsing: Reexamining the role of Broca's area in sentence comprehension. *Cogn Affect Behav Neurosci*. 2005;5(3):263-281. doi:10.3758/CABN.5.3.263

80. Rogalsky C, Matchin W, Hickok G. Broca's area, sentence comprehension, and working memory: an fMRI study. *Front Hum Neurosci*. 2008;2:1-13. doi:10.3389/neuro.09.014.2008

81. Kaan E, Swaab TY. The brain circuitry of syntactic comprehension. *Trends Cogn Sci*. 2002;6(8):350-356. doi:10.1016/S1364-6613(02)01947-2

82. Matchin W. A neuronal retuning hypothesis of sentence-specificity in Broca's area. *Psychon Bull Rev*. 2018;25(5):1682-1694. doi:10.3758/s13423-017-1377-6

83. Rogalsky C, Hickok G. The Role of Broca□s Area in Sentence Comprehension. *J Cogn Neurosci*. 2011;23(7):17.

84. Stowe LA, Haverkort M, Zwarts F. Rethinking the neurological basis of language. *Lingua*. 2005;115(7):997-1042. doi:10.1016/j.lingua.2004.01.013

85. Pettigrew C, Hillis AE. Role for memory capacity in sentence comprehension: Evidence from acute stroke. *Aphasiology*. 2014;28(10):1258-1280. doi:10.1080/02687038.2014.919436

86. Buchsbaum BR, Hickok G, Humphries C. Role of left posterior superior temporal gyrus in phonological processing for speech perception and production. *Cogn Sci*. 2001;25(5):663-678. doi:10.1207/s15516709cog2505_2

87. Baddeley A, Eldridge M, Lewis V. The Role of Subvocalisation in Reading. *Q J Exp Psychol Sect A*. 1981;33(4):439-454. doi:10.1080/14640748108400802

88. Caplan D, Waters GS. Verbal working memory and sentence comprehension. *Behav Brain Sci*. 1999;22(01):77-126. doi:10.1017/S0140525X99001788

89. Caspari I, Parkinson SR, LaPointe LL, Katz RC. Working Memory and Aphasia. *Brain Cogn*. 1998;37(2):205-223. doi:10.1006/brcg.1997.0970

90. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 2004;55(3):335-346. doi:10.1002/ana.10825

91. Gorno-Tempini ML, Brambati SM, Ginex V, et al. The logopenic/phonological variant of primary progressive aphasia. *Neurology*. 2008;71(16):1227-1234. doi:10.1212/01.wnl.0000320506.79811.da

92. Rohrer JD, Caso F, Mahoney C, et al. Patterns of longitudinal brain atrophy in the logopenic variant of primary progressive aphasia. *Brain Lang*. 2013;127(2):121-126. doi:10.1016/j.bandl.2012.12.008

93. Bonner MF, Grossman M. Gray Matter Density of Auditory Association Cortex Relates to Knowledge of Sound Concepts in Primary Progressive Aphasia. *J Neurosci*. 2012;32(23):7986-7991. doi:10.1523/JNEUROSCI.6241-11.2012

94. Hickok G, Poeppel D. Towards a functional neuroanatomy of speech perception. *Trends Cogn Sci*. 2000;4(4):131-138. doi:10.1016/S1364-6613(00)01463-7

95. Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition*. 2004;92(1-2):67-99. doi:10.1016/j.cognition.2003.10.011

96. Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci*. 2007;8(5):393-402. doi:10.1038/nrn2113

97. Rogalsky C, Basilakos A, Rorden C, et al. *The Neuroanatomy of Speech Processing: A Large-Scale Lesion Study*. Neuroscience; 2020. doi:10.1101/2020.04.02.022822

98. Goucha T, Friederici AD. The language skeleton after dissecting meaning: A functional segregation within Broca's Area. *NeuroImage*. 2015;114:294-302. doi:10.1016/j.neuroimage.2015.04.011

99. Matchin W, Hammerly C, Lau E. The role of the IFG and pSTS in syntactic prediction: Evidence from a parametric study of hierarchical structure in fMRI. *Cortex*. 2017;88:106-123. doi:10.1016/j.cortex.2016.12.010

100. Matchin W, Brodbeck C, Hammerly C, Lau E. The temporal dynamics of structure and content in sentence comprehension: Evidence from fMRI-constrained MEG. *Hum Brain Mapp*. 2019;40(2):663-678. doi:10.1002/hbm.24403

101. Pallier C, Devauchelle AD, Dehaene S. Cortical representation of the constituent structure of sentences. *Proc Natl Acad Sci*. 2011;108(6):2522-2527. doi:10.1073/pnas.1018711108

102. Pylkkänen L. Neural basis of basic composition: what we have learned from the red–boat studies and their extensions. *Philos Trans R Soc B Biol Sci*. 2020;375(1791):20190299. doi:10.1098/rstb.2019.0299

103. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014. doi:10.1212/WNL.0b013e31821103e6

104. Mesulam MM, Rogalski EJ, Wieneke C, et al. Primary progressive aphasia and the evolving neurology of the language network. *Nat Rev Neurol*. 2014;10(10):554-569. doi:10.1038/nrneurol.2014.159

105. Battistella G, Henry M, Gesierich B, et al. Differential intrinsic functional connectivity changes in semantic variant primary progressive aphasia. *NeuroImage Clin*. 2019;22:101797. doi:10.1016/j.nicl.2019.101797

106. Kielar A, Deschamps T, Jokel R, Meltzer JA. Abnormal language-related oscillatory responses in primary progressive aphasia. *NeuroImage Clin*. 2018;18:560-574. doi:10.1016/j.nicl.2018.02.028

107. Mummery CJ, Patterson K, Wise RJS, Vandenbergh R, Price CJ, Hodges JR. Disrupted temporal lobe connections in semantic dementia. *Brain*. 1999;122(1):61-73.

108. Ranasinghe KG, Hinkley LB, Beagle AJ, et al. Distinct spatiotemporal patterns of neuronal functional connectivity in primary progressive aphasia variants. *Brain*. 2017;140(10):2737-2751. doi:10.1093/brain/awx217

109. Sonty SP, Mesulam MM, Thompson CK, et al. Primary progressive aphasia: PPA and the language network. *Ann Neurol*. 2003;53(1):35-49. doi:10.1002/ana.10390

110. Sonty SP, Mesulam MM, Weintraub S, Johnson NA, Parrish TB, Gitelman DR. Altered Effective Connectivity within the Language Network in Primary Progressive Aphasia. *J Neurosci*. 2007;27(6):1334-1345. doi:10.1523/JNEUROSCI.4127-06.2007

111. Wilson SM, Brambati SM, Henry RG, et al. The neural basis of surface dyslexia in semantic dementia. *Brain*. 2009;132(1):71-86. doi:10.1093/brain/awn300

112. Faria AV, Sebastian R, Newhart M, Mori S, Hillis AE. Longitudinal imaging and deterioration in word comprehension in primary progressive aphasia: Potential clinical significance. *Aphasiology*. 2014;28(8-9):948-963. doi:10.1080/02687038.2014.911241

113. Mesulam MM, Wieneke C, Hurley R, et al. Words and objects at the tip of the left temporal lobe in primary progressive aphasia. *Brain*. 2013;136(2):601-618. doi:10.1093/brain/aws336

114. Dunn L, Dunn L. *Peabody Picture Vocabulary Test-4*. Pearson; 2007.