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Adaptive significance of right hemisphere activation in aphasic language comprehension

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Abstract

Aphasic patients often exhibit increased right hemisphere activity during language tasks. This may represent takeover of function by regions homologous to the left-hemisphere language networks, maladaptive interference, or adaptation of alternate compensatory strategies. To distinguish between these accounts, we tested language comprehension in 25 aphasic patients using an online sentence-picture matching paradigm while measuring brain activation with MEG. Linguistic conditions included semantically irreversible (“The boy is eating the apple”) and reversible (“The boy is pushing the girl”) sentences at three levels of syntactic complexity. As expected, patients performed well above chance on irreversible sentences, and at chance on reversible sentences of high complexity. Comprehension of reversible non-complex sentences ranged from nearly perfect to chance, and was highly correlated with offline measures of language comprehension. Lesion analysis revealed that comprehension deficits for reversible sentences were predicted by damage to the left temporal lobe. Although aphasic patients activated homologous areas in the right temporal lobe, such activation was not correlated with comprehension performance. Rather, patients with better comprehension exhibited increased activity in dorsal fronto-parietal regions. Correlations between performance and dorsal network activity occurred bilaterally during perception of sentences, and in the right hemisphere during a post-sentence memory delay. These results suggest that effortful reprocessing of perceived sentences in short-term memory can support improved comprehension in aphasia, and that strategic recruitment of alternative networks, rather than homologous takeover, may account for some findings of right hemisphere language activation in aphasia.

Keywords

Language; Aphasia; Magnetoencephalography; Stroke; Syntax

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Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2013.03.007>.

1. Introduction

A central theme in neuroimaging research on aphasia is the takeover of language functions by alternative brain networks. Numerous studies have revealed increased brain activity in the right hemisphere (RH) in aphasics relative to healthy controls during performance of language tasks. However, the significance of these findings is poorly understood. Some evidence suggests that it represents adaptive plasticity, in which the homologous RH regions take over the original functions of the damaged left hemisphere (LH) (Blasi et al., 2002; Ohyama et al., 1996; Thulborn, Carpenter, & Just, 1999; Winhuisen et al., 2005). Other studies have suggested that RH activation may actually be maladaptive, a result of overexcitation related to the loss of transcallosal inhibition from the damaged LH (Heiss, Thiel, Kessler, & Herholz, 2003; Postman-Caucheteux et al., 2010; Price & Crinion, 2005). The common finding that increased RH activation is associated with larger lesions and more severe aphasia (Heiss & Thiel, 2006; Karbe et al., 1998; Rijntes, 2006) can be accommodated by either account, as patients with less remaining healthy tissue in the LH may be forced to employ the RH even if it is a less effective language processor than the original areas.

A third possibility, not mutually exclusive with the first two, is that activation in atypical regions reflects a shift to a qualitatively different strategy for language processing. This account is perhaps the most intriguing, as brain imaging results may be able to help identify the strategies underlying better recovery, and thus inform treatment efforts. Evidence of compensatory shifts in strategy could take the form of a significant correlation between neural activity and performance in regions that are not typically activated in healthy controls. These correlations may occur in RH regions that are symmetrical to typical control regions, suggesting homologous takeover, or they may instead occur in distinct regions of the RH, suggesting strategic recruitment.

To investigate these alternative hypotheses, we conducted a brain imaging study of sentence comprehension in aphasic patients, using stimuli that are known to elicit a broad range of performance in these patients. We used a sentence-picture-matching task, and measured brain activation while subjects listened to sentences of various degrees of difficulty, and during a delay period while subjects retained the sentences in short-term memory prior to picture presentation. We previously used this task in two studies with young healthy control subjects, employing both functional magnetic resonance imaging (fMRI; Meltzer, McArdle, Schafer, & Braun, 2010) and magnetoencephalography (MEG; Meltzer & Braun, 2011). We found that MEG was able to reveal patterns of neural activation that closely matched fMRI results in the same subjects, but the superior temporal resolution of the technique allowed us to dissociate activity occurring in the successive stages of perception and retention of sentences. Therefore, we used MEG here to investigate relationships between functional activation and comprehension in aphasia.

Our studies of sentence-picture-matching employ two factors that modulate the difficulty of the task. One factor is semantic reversibility. Reversible sentences (e.g. “The boy is pushing the girl”) require explicit attention to syntactic cues (in English, chiefly word order) to determine the thematic roles of the nouns mentioned in the sentence, whereas the meaning of an irreversible sentence (e.g. “The boy is eating the apple”) is clear from the semantic constraints of the nouns involved.

A second factor is syntactic complexity. Complexity of sentences can be defined in numerous ways, but we focused on one particular contrast that has been studied extensively. In English, the agent of an action tends to precede its patient e.g. “The boy [AGENT] is pushing the girl [PATIENT].” Sentences that violate this tendency are considered more

complex. Typical syntactic structures with reversed AGENT-PATIENT word order include passive voice (“The boy is pushed by the girl”) and object-embedded relative clauses (defined below). To test for effects of syntactic complexity, we compared two kinds of sentences: those with more complex object-embedded relative clauses (example 1, traditionally abbreviated “SO” as the first noun is the *subject* of the main clause but *object* of the relative clause) and those with less complex subject-embedded relative clauses (example 2, abbreviated “SS” as the first noun is the subject of both clauses).

1. (SO) The boy who the girl is pushing wants to win the race.
2. (SS) The boy who is pushing the girl wants to win the race.

Using fMRI, we observed that reversible sentences induced larger hemodynamic responses throughout the left-hemisphere perisylvian cortex, regardless of syntactic complexity (Meltzer et al., 2010). Effects of syntactic complexity occurred almost exclusively within reversible sentences only, as the meaning of irreversible sentences can be easily determined from semantic constraints alone. Reversible complex sentences induced larger hemodynamic responses in frontal areas related to language and working memory. In MEG (Meltzer & Braun, 2011), we observed essentially the same effects, but we were able to measure the timecourse of these effects more precisely. We found that the effects of reversibility began during sentence presentation and persisted throughout the 3-second memory delay period between sentence offset and picture onset, but complexity effects occurred *only* during the post-sentence delay. This finding suggests that the increased processing demands of syntactically complex sentences may be primarily driven by posthoc reanalysis in working memory, rather than specialized mechanisms of syntactic comprehension that are automatically triggered by certain structures.

The activation seen in our MEG study of sentence-picture-matching took the form of event-related desynchronization (ERD, i.e. power decrease) of ongoing oscillations, primarily in the frequency range of 8–30 Hz, comprising the alpha and beta bands as traditionally defined. The spatial distribution of these effects corresponded closely to patterns of blood oxygen level-dependent (BOLD) signal seen in fMRI data acquired from the same subjects. This is consistent with other studies that have shown a colocalized inverse relationship between BOLD and MEG signal power in these frequency bands (Brookes et al., 2005; Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005; Singh, Barnes, Hillebrand, Forde, & Williams, 2002). Thus, mapping alpha/beta ERD in MEG is emerging as an attractive alternative to fMRI for certain studies. In the present study, we used this technique to reveal relationships between language comprehension, lesion extent, and compensatory neural activity.

2. Methods

2.1. Participants

We recruited 25 participants (14 male, 11 female), all of whom had suffered a single left-hemisphere ischemic stroke at least 6 months previously, resulting in aphasia. All patients passed an audiometric evaluation, and retained sufficient capacity of language comprehension to consent to the procedures and follow task instructions. Patients ranged in age from 34–72 years (mean=57). The study was approved by the Institutional Review Board of the NIH Intramural Program (NIH protocol 92-DC-0178). Participants were financially compensated.

Although the primary goal of this study was to explore relationships between behavioral and imaging measures *within* the group of aphasic patients, it was also instructive to compare the aphasics as a group to healthy control subjects. From our previous MEG study (Meltzer &

Braun, 2011), we had a large body of MEG data from young, healthy controls performing the exact same task paradigm, of approximately equal size as the patient group (24 young controls). We elected to use this data for direct comparison with the patient group, mainly due to the large sample size available. However, it is possible that differences between the patient group and the younger controls may be confounded by age differences between the groups. To explore potential effects of age, we recruited an additional group of nine healthy older adults (range 44–71, mean=53). The older controls were matched in age to the patients (2-sample t test, $t(18.8)=1.09$, $p=0.29$). Older controls tended to have more years of education than aphasic patients (means 19.8 vs. 16.8, $t(12.1)=2.45$, $p=0.03$). However, the older controls in this respect are more comparable to the young controls, who, as is typical in neuroimaging experiments, were mostly undergraduate and graduate students in the middle of attaining a high degree of education. Age-matched control subjects participated in all behavioral and neuroimaging assessments completed by the patients, whereas the younger controls only completed the neuroimaging components. All control subjects tested within normal limits on all cognitive and linguistic tests. Comparisons between patients and age-matched controls, and between younger and older controls, are presented in Supplementary information.

2.2. Behavioral assessment

Prior to participation in the MEG experiment, patients and age-matched controls were administered an extensive battery to assess behavioral deficits. Tests included the Western Aphasia Battery (Kertesz, 1982) for primary diagnosis of aphasia type, supplemented by selected portions of the PALPA exam (Psycholinguistic Assessments of Language Processing in Aphasia, Kay, Coltheart, & Lesser, 1992) and the Object & Action Naming Battery (Druks & Masterson, 2000) for further examination of linguistic abilities. Scores on selected subtests were combined into composites reflecting abilities for repetition, receptive lexical semantics, and expressive lexical semantics. See Table 1 for scores in each patient and details of the composites. Additionally, we administered three tests to rule out low-level sensory and semantic deficits that could potentially account for poor performance on the main experimental task. The BORB (Birmingham Object Recognition Battery, Riddoch & Humphreys, 1993) was used to assess visual object recognition, a necessary skill for the sentence-picture-matching task used in the present experiment. The NTAP (Nonverbal Test of Auditory Processing, Saygin, Dick, Wilson, Dronkers, & Bates, 2003) was used to assess pre-linguistic deficits in auditory processing, and the PPT (Pyramids and Palm Trees Test, version 1, picture-picture matching, Howard & Patterson, 1992) was used to assess semantic knowledge independent of lexical access. No patients were excluded on the basis of lower level deficits. All patients made two or fewer errors out of 32 and 20 on the BORB and NTAP, respectively, while the minimum score in our group on the PPT was 42 out of 52. The fact that aphasic participants had preserved abilities for audio-visual and semantic processing is reflected by their uniformly good performance on the sentence-picture-matching task when sentences were not semantically reversible (see results). For an offline assessment of sentence comprehension, we administered a sentence-picture-matching task different than the one used in the MEG experiment, consisting of 40 sentences of various structures (Psycholinguistic Assessment of Language (PAL) provided by David Caplan).

We originally recruited 26 patients, but one patient, who had been diagnosed with Broca's aphasia immediately after a stroke, was excluded due to testing within normal limits on the WAB and having only a very small lesion confined to the temporal lobe, leaving 25 patients in the experimental group.

2.3. Anatomical MRI

Each patient underwent an anatomical MRI session, for purposes of MEG source localization and lesion delineation. Anatomical MRIs were always acquired after the MEG session, most often on the same day, but occasionally up to a week later. MRI was acquired on a General Electric Signa 3-Tesla scanner with an 8-channel head coil, using parallel imaging with ASSET reconstruction. Scans included a T1-weighted 3D high-resolution MPRAGE (1 mm isotropic resolution, Fast Spin-Echo T2, T2 FLAIR (both 3.5 mm thick slices), and DTI (not reported here). T1 images were skull stripped by applying a stripping procedure to the T2-weighted image, applying the resulting mask to the T1 image, and making further manual adjustments. This procedure produces better results than stripping the T1 image directly, due to the presence of large lesions that appear dark on T1 contrast.

Lesion borders were delineated using segmentation tools in FSL and region of interest (ROI) drawing tools in AFNI, based on a T1 intensity threshold followed by manual adjustments. Regions of gliosis were included in the lesion on the basis of hyperintense signal seen in a coregistered T2-FLAIR image. T1 images were spatially normalized by computing a 12-parameter affine registration between the individual patient brains and the “Colin brain,” a single subject template, in Talairach space. Nonlinear registration algorithms produced slightly better registrations in some cases, but were not reliable for all patients in the presence of large lesions, so affine registration was adapted for consistency across the cohort. Cost-function masking was applied using the individual lesion masks to exclude the lesioned area from the warp computation. Using the computed affine matrices, both T1 anatomical images and lesion masks were warped into Talairach space for group analysis of lesion characteristics and source-localized MEG activation.

For display of activation maps derived from patient data, we constructed a “composite lesion underlay” to help indicate the regions that tended to be damaged in the patient group. The spatially normalized T1-weighted anatomical images of the 25 patients were averaged together. The resulting image was further darkened by subtracting a percentage of the signal proportional to the number of patients having a lesion at each voxel.

2.4. Voxel-wise and ROI-based lesion-symptom correlations

Given the considerable variation in language comprehension performance and lesion location/extent across the patient group (see results), we quantitatively assessed the relationship between these variables using two techniques. First, we employed voxel-based lesion symptom mapping (VLSM; Bates et al., 2003), implemented in the *MRICron* software (Rorden, Karnath, & Bonilha, 2007). The relationship between behavioral performance and lesion location was tested on a voxel-wise basis using a 2-sample *t* test. Briefly, at each voxel, the behavioral scores were compared between the group of patients with a lesion at that voxel and those without, resulting in different group sizes at different voxels depending on the individual lesion patterns. Because each voxel used a *t* test with varying degrees of freedom, the resulting scores were converted to *Z*-scores of equivalent *p*-value prior to cluster-level correction. We limited inference to voxels that were lesioned in at least 5 out of the 25 patients.

VLSM can provide high spatial resolution, mapping lesion-deficit patterns down to the level of single voxels. However, inference on the voxel level requires adequate correction for multiple comparisons across all the voxels tested, raising the required sample size to achieve reasonable statistical power. Typically, VLSM studies in the literature have used sample sizes much larger than what is typical in functional neuroimaging studies, in the range of 40–80 patients. Our sample of 25 is too low for voxel-wise statistical inference, but can still provide reasonable power on the level of larger clusters. Correction based on cluster extent

(Forman et al., 1995) provides increased sensitivity at a cost of resolution: one can only say that the cluster as a whole is significant, rather than individual voxels within it. We applied the cluster-correction algorithm implemented in the AFNI program *Alphasim*, which is based on Monte Carlo simulations that estimate the probability of obtaining a cluster of a given size or greater, given a voxel-wise statistical threshold and an estimate of smoothness of the input data. First, we used the AFNI program 3dFWHMx to estimate the smoothness of the lesion maps within the region tested, obtaining an average full width at half-maximum of 3.44 mm. This value was used in *Alphasim* for Monte Carlo simulations to estimate the cluster size required for a family-wise error rate of $p < 0.05$, using a voxel-wise threshold of $p < 0.05$. The resulting cluster size was 786 mm³.

Because our use of cluster-level correction in VLSM is non-standard, we also conducted an ROI-based analysis of relationships between lesion extent and comprehension performance. This analysis tests for correlations between a behavioral measure and the percentage of lesion overlap with several ROIs. Using the macroanatomical cortical parcellation of Tzourio-Mazoyer et al. (2002), implemented in AFNI as the “macrolabels” atlas, we selected 13 left-hemisphere cortical regions that tended to be damaged in some but not all patients. For each region, we computed the percentage of overlap between each patient’s lesion mask (warped into Talairach space) and the ROI. We then computed behavioral correlations for each region, and applied Bonferroni correction across regions ($p = 0.05/13 = 0.0038$) to select a threshold for statistical significance.

2.5. Sentence picture-matching paradigm

Patients performed a sentence picture-matching task during MEG scanning, providing a measure of neural activity related to comprehension of sentences and maintenance of sentence content in short-term memory. Complete details of the sentence and picture materials can be found in our previous report from young healthy controls, which used the same paradigm (Meltzer & Braun, 2011). A brief description of the paradigm is given here. Trial structure is diagramed in Fig. 1A. On each trial, subjects heard a sentence, spoken at a natural rate, while viewing a fixation cross. The average length of auditory sentences was 3.5 s. After the sentence, the fixation cross remained during a three-second memory delay. Next, the cross was replaced by two pictures. Subjects indicated which picture correctly depicted the action described in the sentence, by pressing the left or right button on a fiberoptic response box. The subject’s choice was indicated by outlining the selected picture in a green box, but no feedback on accuracy was given. Pictures remained on screen for 4 s, and were followed by a variable inter-trial interval of 2.1–2.25 s. All responses occurring before the onset of the next trial were scored, but visual feedback (the green highlighting) was only provided while the pictures were onscreen. Trials were presented in seven runs of 36 trials each, and subjects were allowed to rest in between runs if desired. Total time for the experiment was approximately one and a half hours, including preparation.

Two hundred and fifty two sentences were used for this experiment, in 6 categories, for a 2×3 factorial design (semantic reversibility × syntactic complexity). All conditions were matched for sentence length in words and syllables. All sentences involved one or two out of four possible people, namely “the boy, the girl, the man, and the woman.” Reversible sentences (R) involved a human as both subject and object, and were constructed to avoid plausibility biases. Irreversible sentences (I) involved one human and one inanimate object. Three levels of syntactic complexity were employed, with examples shown in Table 2. Each sentence was decomposable into three prosodic units, indicated by slashes in Table 2. Digital triggers were manually inserted into the wav files at the boundaries between the three sentence regions, delineating the pre relative clause segment (“Pre-RC”), the relative clause (“RC”), and the post-relative-clause segment (“Post-RC”), as shown in Fig. 1B. These triggers were inserted into the MEG acquisition stream to allow for analysis of

activity within particular regions of the sentence, and also for activity occurring in the memory delay following the sentence. Note that the terminology we have chosen for the sentence segments is not strictly applicable to the simple active sentences, which do not contain a relative clause, but we retain it for consistency, as these sentences were prosodically similar to the other conditions.

For each group of six sentences involving a particular verb, we produced four photographs for the picture-matching task (Fig. 1C and D). The photographs all involved the same set of four actors (man, woman, boy, and girl). Subjects were familiarized with the actors before the experiment so that they could clearly distinguish them. For a reversible sentence such as “The boy who the girl is pushing hopes to win the race,” the target picture depicted a girl pushing a boy, while the syntactic foil depicted a boy pushing a girl. For trials with syntactic foils, it is necessary to use syntactic information to assign thematic roles correctly, as the same two people are mentioned in the sentence. Lexical foils involved a person not mentioned in the sentence, depicting e.g. a girl pushing a woman, or a woman pushing a girl. For irreversible sentences, only lexical foils were used, but either the human agent or the inanimate patient could be substituted. For reversible sentences, half of the picture pairs involved a syntactic foil, and half a lexical foil. For irreversible sentences, half of the pictures involved a substitution of the human agent, and half of the inanimate patient. Thus, for behavioral purposes, there were a total of 12 conditions (2 reversibility $\times$ 3 complexity $\times$ 2 foil type), with 21 trials of each. However, since the subjects did not know which type of foil would appear on each trial, EEG-MEG analysis of brain activity occurring prior to picture onset was collapsed across foil types, yielding 42 trials per condition.

2.6. MEG acquisition and analysis

MEG was recorded with a CTF Omega 2000 system, comprising 275 first order axial gradiometers. For environmental noise reduction, synthetic third-order gradiometer signals were obtained through adaptive subtraction of 33 reference channels located inside the MEG dewar far from the head. Signals were digitized at 600 Hz with an anti-aliasing filter at 125 Hz. Head position was tracked continuously using coils placed at three fiducial points on the head (McCubbin et al., 2004). The average head position over the entire experiment was used for source localization, and coregistered with the same fiducial points marked on the anatomical MRI using adhesive marker disks. In no cases did the total movement RMS for any coil exceed 1 cm.

MEG data were analyzed in the frequency domain using Synthetic Aperture Magnetometry (SAM), (Sekihara, Nagarajan, Poeppel, Marantz, & Miyashita, 2001; Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997; Vrba & Robinson, 2001), as implemented in CTF software (CTF, Port Coquitlam, British Columbia, Canada). At a regular grid of locations spaced 7 mm apart throughout the brain, we computed the pseudo-T value, which is a normalized measure of the difference in signal power between two time windows (Vrba & Robinson, 2001). Maps of pseudo-T values throughout the brain were spatially normalized to Talairach space using the same transformations applied to the T1-weighted anatomical image (see below), allowing for group-level statistics applied to these values.

The SAM technique compares oscillatory power during different time periods of interest (defined in the results section) at specific locations in the brain, while employing a spatial filtering algorithm to cancel activity generated in other regions. In practice, the procedure yields a map of neural activity in the brain similar to fMRI or PET, but typically with somewhat less spatial resolution. The actual resolution depends on the data, including the frequency band used for analysis (Brookes et al., 2008). Based on our previous results in healthy controls (Meltzer & Braun, 2011), we used a frequency band of 8–30 Hz for all analyses. Neural activity generally results in a decrease in oscillatory power in this range

(Brookes et al., 2005; Hillebrand et al., 2005; Singh et al., 2002), so negative values in our SAM results tend to correspond to positive BOLD activations observed in the same task (Meltzer et al., 2010).

Spatially normalized SAM pseudo-T values computed on the individual subject level were subjected to group-level analyses, including one-sample *t* tests for activation maps, and Spearman's rank-order correlation test for correlations with performance. The final results were corrected for multiple comparisons across voxels using the same cluster-level threshold procedure used for the VLSM maps. The cluster size criterion was determined by Monte Carlo simulations conducted in the AFNI program *Alphasim*, using an estimated spatial smoothness value of 8 mm FWHM. This value was derived by computing a "null hypothesis" SAM map comparing the pre-stimulus period between two different sentence conditions (which should not differ). Two such null maps computed from separate sets of trials agreed on a smoothness value of approximately 8 mm. All activation maps within groups were thresholded at a voxel-wise level of $p < 0.01$, and a cluster-wise corrected value of $p < 0.05$. For comparisons between patients and controls, and correlations with performance, a more liberal voxel-wise threshold of $p < 0.025$ was used, but cluster-wise values were still controlled at $p < 0.05$. These voxel-wise thresholds are somewhat lower than we typically use in MEG studies of language processing in healthy controls (cf. Meltzer & Braun, 2011, and more recent studies in preparation), due to the higher degree of variability in activation patterns seen in patients with different lesions, and the search for subtle differences between subject groups. Although the statistical inference is equally valid, the price paid for greater sensitivity is poorer anatomical resolution. Larger clusters are required to obtain statistical significance, and it is impossible to assign special importance to individual voxels within the cluster, potentially resulting in more distributed patterns of activity.

3. Results

3.1. Sentence comprehension performance

Patients exhibited a graded pattern of comprehension performance related to the factors of reversibility and syntactic complexity, with a large amount of individual variation in certain conditions. Average percent incorrect trials (including both wrong responses and non-responses) for each of 12 conditions are presented in Fig. 2A. Within the irreversible category (right half of the figure), comprehension performance was essentially constant between the different trial conditions, and consistently good. A repeated measures ANOVA on error rates for irreversible sentences revealed no significant effects of syntactic complexity [$F(2,48)=0.169$, *ns*] or foil type [$F(1,24)=0.6311$, *ns*], and only a marginal interaction between the two [$F(2,48)=3.123$, $p=0.053$]. In contrast, within the reversible sentences, there were robust effects of both syntactic complexity [$F(2,48)=26.8$, $p < 10^{-7}$] and foil type [$F(1,24)=56.1$, $p < 10^{-7}$], and a highly significant interaction [$F(2,48)=18.2$, $p < 10^{-5}$], reflecting the special difficulty caused by the RSO sentences paired with syntactic foils. Furthermore, reversible sentences are comprehended more poorly than irreversible sentences regardless of foil type. Collapsing across foil type, a repeated measures ANOVA testing factors of reversibility and syntactic complexity revealed highly significant effects of both reversibility [$F(1,24)=173.0$, $p < 10^{-11}$], syntactic complexity [$F(2,48)=30.0$, $p < 10^{-8}$], and an interaction between the two [$F(2,48)=17.6$, $p < 10^{-5}$].

The nature of these effects can be appreciated by inspection of Fig. 2A. The relatively constant error rates across the irreversible conditions can be seen in the right half of Fig. 2A. Performance on the irreversible sentences was uniformly good, well above chance level (50%) in all participants. The reversible sentences, in which thematic roles had to be determined by sentence structure, presented a greater challenge. In particular, trials with

syntactic foils, in which the same participants were shown with thematic roles reversed, induced chance comprehension performance in a subset of patients. The greatest challenge was with the syntactically complex RSO sentences, in which the average performance in the entire group fell to chance level. These findings contrast sharply with those in healthy control subjects (Meltzer & Braun, 2011), in which error rates were approximately 4% in the RSO condition and about 2% in other conditions.

Although the average error rates suggest an intermediate degree of comprehension performance for the RSS and RAC sentences, examination of response patterns across the patient population reveals striking individual variability. Based on the average results, we pooled together conditions that were not significantly different from each other, generating three general categories, for which individual scores from every patient are plotted in Fig. 2B. All irreversible sentences were pooled together, regardless of foil type. Within the reversible conditions, RSO sentences with syntactic foils were considered as a category of their own, labeled “reversible complex.” RSS and RAC conditions with syntactic foils were considered together as “reversible non-complex,” as comprehension of the two sentence structures did not differ within participants [paired $t(24)=0.62$, *ns*]. Reversible sentences with lexical foils were not considered for this analysis, as the lexical foils do not test comprehension of thematic roles. Inspection of these individual scores reveals that irreversible sentences were uniformly comprehended well by all patients. Reversible complex sentences were comprehended poorly by all patients, with very few patients scoring statistically above chance (fewer than 33% incorrect for $p < 0.05$). Some patients scored statistically below chance, reflecting a systematic strategy on RSO sentences of selecting the first noun as the agent – these patients tended to be *less* impaired than those scoring at chance. For reversible non-complex sentences, there was a fairly uniform distribution of performance, ranging from perfect (0 errors) to chance (50% errors). These conditions seem to best reflect individual differences in sentence comprehension ability across a cohort of aphasic patients. Therefore, we selected performance on reversible non-complex sentences for further scrutiny as a measure of syntactic comprehension, hereafter referred to by the abbreviation SynComp. To render a more interpretable score (higher numbers reflecting better comprehension), performance scores were chance-corrected using a standard formula for two-alternative forced-choice tests (Frary, Cross, & Lowry, 1977), yielding a value of one for perfect performance and zero at chance comprehension levels.

$$\text{SynComp} = \text{Proportion correct} - (\text{Proportion incorrect}) / (\text{choices} - 1) = 1 - 2 (\% \text{ Proportion incorrect})$$

Note that non-responses (fewer than 1.5% of all trials) were considered incorrect, as subjects were encouraged to respond to all trials even if they were not entirely sure of the correct answer. The SynComp variable was used as the primary measure characterizing comprehension performance across the patient cohort for correlations with lesion location and MEG activity.

We also assessed reaction time patterns in the patients across the different conditions. Results were similar to those previously obtained in control subjects, and are shown in supplementary information.

3.2. Additional correlations between behavioral and lesion characteristics

We examined correlations between SynComp and offline behavioral measures resulting from language testing, as well as lesion characteristics. Scatterplots of the relationship between these measures are shown in Fig. 3. To avoid possible problems related to nonlinearity or nonnormality in our imaging and behavioral measures, we used Spearman's rank-order nonparametric correlation test for all correlation analyses. Spearman's Rho coefficient (ρ) is roughly equivalent to a parametric correlation coefficient. Fig. 3A presents

the relationship between SynComp and the Aphasia Quotient (AQ) of the Western Aphasia Battery (WAB), an overall measure of aphasia severity that is considerably weighted towards production abilities rather than comprehension. A slight positive relationship is apparent, but it is of only marginal significance [$r = 0.34$, $p = 0.09$]. However, the correlation with the Auditory-verbal Comprehension (AVC) subscore of the WAB was much stronger, as shown in Fig. 3B, [$r = 0.64$, $p < 0.001$]. This suggests that sentence picture-matching performance on reversible non-complex sentences is a reasonable proxy for overall language comprehension variability in aphasic patients. A strong correlation was also observed between the SynComp score and the score on the PAL sentence-picture matching test administered during offline testing [$r = 0.49$, $p < 0.014$] (data not shown).

We also explored the relationship between these behavioral measures and total lesion size, defined as the percentage of the left cortex lesioned, based on the macrolabel atlas. We did not include subcortical lesion extent in this definition of lesion size, due to the difficulty in distinguishing between white matter and gray matter lesion extent. Furthermore, subcortical structures such as the basal ganglia tend to suffer more severe distortions of shape in post-stroke brains, and we were less confident in the quality of the affine registrations for yielding good overlap of subcortical nuclei in the patient group. There was a strong negative correlation between AQ and lesion size [$r = -0.53$, $p < 0.01$], reflecting the intuitive notion that patients with larger lesions tend to suffer more severe aphasia in general (Fig. 3C). However, no significant relationship was present between SynComp and lesion size [$r = -0.24$, $p = 0.25$] (Fig. 3D). However, it is likely that individual variability in comprehension may be explained by patterns of damage to more specific brain regions, as well as differences in compensatory brain activation in other areas. We tested these hypotheses using more detailed analyses of lesion location, as well as MEG data, as described below.

3.3. Language impairment and lesion variability

We used the VLSM technique (see methods) to evaluate the relationship between lesion location and language impairment, on the behavioral variables discussed above. Fig. 4A shows the degree of lesion overlap across the entire patient cohort. Voxels lesioned in 1–4 patients are shown in green; these were not included in the VLSM analyses. Orange to yellow colors indicate higher overlap of 5–21 patients. Lesion overlap was maximal in the frontal lobe insula and subcortical region. This distribution is to be expected, reflecting the typical distribution of Middle Cerebral Artery infarcts (Phan, Donnan, Wright, & Reutens, 2005), the most common cause of aphasia.

Fig. 4B shows the VLSM results from the analysis of the SynComp (syntactic comprehension) variable. This yielded one significant cluster, which was confined largely to the temporal lobe, mainly in the middle temporal gyrus, but extending into the superior temporal gyrus and the angular gyrus in the inferior parietal lobe. Given the limitations of VLSM applied on the cluster level (see methods), we supplemented this analysis by computing correlations between SynComp and lesion percentage in 13 ROIs. Correlations and p -values are shown in Table 3. The results are highly consistent with the VLSM analysis. There was a highly significant correlation in the left middle temporal gyrus, and a lesser but still significant one in the angular gyrus. The only other region approaching significance was the superior temporal gyrus ($p = 0.06$).

We also conducted VLSM analysis on some additional behavioral measures for comparison; these are presented in Supplementary information (Fig. S1).

3.4. MEG activity—reversibility

Analysis of task-related MEG activity involves numerous options for selecting time windows, frequency bands, and conditions to compare. To narrow down these choices, we are guided by our previous results in healthy controls (Meltzer & Braun, 2011). In that study, we did not observe any significant differences between sentence conditions in the pre-RC and RC portions of the sentence. Therefore, we confine our analyses here to time windows when significant effects were detected in controls, including the post-RC sentence period (see Fig. 1B) and the subsequent memory delay. Based on our previous results, neural “activation” is measured by power *decrease* (i.e. event-related desynchronization) in a frequency range of 8–30 Hz. Note that because our primary measure of interest is a power *decrease*, our activation maps are plotted mainly in blue, reflecting the negative values. Red voxels represent power *increases*, which are associated with a *reduction* in neural activity.

To reveal activity specifically related to comprehending sentence structure (including thematic roles, i.e. who did what to whom), we contrasted all reversible sentences (RSS, RSO, and RAC) minus irreversible sentences (ISS, ISO, IAC). Contrasts limited to subsets of these conditions, such as canonical word order only (RSS+RAC minus ISS+IAC), or relative-clause sentences only (RSS +RSO minus ISS+ISO) generated nearly identical results, so we chose to present the contrast using the maximum amount of data.

Fig. 5A presents the activation map for reversible minus irreversible sentences in young controls, during the post-RC sentence portion and the subsequent memory delay. In both time periods, reversible sentences induce increased activation in left frontal, temporal, and inferior parietal regions, with the activation pattern extending to more frontal areas during the memory delay period. These findings were reported previously in Meltzer and Braun (2011), although they are presented here with a more liberal statistical threshold to be more comparable to the maps obtained in patients, who exhibit considerably more variability due to their individual lesion patterns.

In aphasic patients, as expected, much less activity was observed in the lesioned left hemisphere. Fig. 5B presents the average activation maps in the patient cohort, while Fig. 5C shows the subtraction map of patients minus controls. These maps show a lack of activation in left-hemisphere fronto-temporal regions in the patient cohort, reflected by the *positive* values in the subtraction map. In contrast, patients exhibit extensive activation in the right hemisphere, in parietal, temporal, and frontal regions. However, due to primarily increased variability in the patient group, relatively little of the right hemisphere activity in the patient group reaches statistical significance in the comparison with the control group. Exceptions include the right temporo-parietal-occipital junction during sentence presentation, and the right IFG during the memory delay. Similarly, no significant increase in right hemisphere activity is observed when comparing patients to older controls (Supplementary information, Fig. S3). However, activity that is systematically increased in the entire patient group may not be as relevant for recovery as activity that is correlated with comprehension performance across patients. We explore the latter question with subsequent analyses described below.

3.5. MEG activity—syntactic complexity

In our previous MEG study with young healthy controls (Meltzer & Braun, 2011), we found that the syntactically complex reversible sentences (RSO condition) induced increased activity in bilateral frontal regions, but only during the memory delay period, not during the actual sentence presentation. In the present study, all patients exhibited marked comprehension deficits for RSO sentences, typically performing at chance levels when these sentences were followed by syntactic foils. To examine whether patients exhibited any

additional activation for these complex sentences that they failed to comprehend, we computed statistical maps for the contrast RSO-RSS, during the post-RC sentence period and the memory delay (note that foil type is not relevant for the MEG analysis, because the data are acquired from task periods that precede the picture presentation). Most of the individual patients did not exhibit any significant activation for this contrast at all, and no significant clusters were detected on the group level (data not shown). The direct subtraction of patients minus controls yields significantly more activation in controls, throughout bilateral frontal regions (data not shown—the pattern is essentially identical to the activation map in controls).

3.6. MEG correlation with performance

Although patients consistently failed to comprehend the most complex sentences (RSO condition), while performing well on the irreversible sentences, the conditions of intermediate difficulty (RSS and RAC, together comprising the “SynComp” score) yielded considerable variability in performance (Fig. 2). To test whether this variability was related to differences in brain activation, we tested for voxel-wise rank-order correlations (Spearman’s Rho) across patients between the SynComp scores and MEG activation for the reversible minus irreversible contrast. Clusters of significant correlation were detected in both the post-RC sentence period and the memory delay, as shown in Fig. 5D. During the sentence, activation in bilateral posterior temporal and parietal regions was predictive of greater comprehension performance. During the memory delay, significant correlations with performance were seen only in the right hemisphere. Significant clusters included one centered in the right superior and middle frontal gyri, and a larger cluster in the superior and inferior parietal lobes.

Although activity correlated with comprehension performance was detected, it is interesting to note that none of the regions exhibiting the correlation are “classical” perisylvian language areas. One possible problem with the voxel-wise approach to testing correlations is that the overall level of activation in language regions might in fact correlate with performance, but vary in exact position across patients enough to preclude detection on a voxel-wise level. Therefore, we also conducted an ROI-based analysis, presented in Supplementary information (Fig. S4). This analysis led to the same conclusion, with comprehension performance across patients correlating only with activity in more dorsal frontal-parietal regions.

4. Discussion

4.1. Syntactic comprehension in aphasia

Comprehension of complex syntactic constructions has historically been a central topic in neurolinguistics. Numerous studies have showed that aphasic patients have pronounced difficulty understanding reversible sentences that are syntactically complex, with complexity defined operationally as a non-canonical word order (PATIENT before AGENT) (Berndt, Mitchum, & Wayland, 1997). However, a lively controversy has raged on the specific relationship between selective comprehension failure on complex sentences and damage to particular brain regions (Caramazza, Capitani, Rey, & Berndt, 2001; Drai & Grodzinsky, 1999, and many others). Of the sentence types described above, the object-relative clauses used as the complex condition in our study are known to be the most difficult (Berndt et al., 1997; Sherman & Schweickert, 1989). Some authors have suggested that the comprehension failure stems not from a loss of specialized syntactic processing mechanisms, but rather a depletion of more general-purpose cognitive resources required to handle the working memory demands of such sentences (Caplan, Waters, Dede, Michaud, & Reddy, 2007).

Our data appear to support the resource depletion account, in that every single one of our patients exhibited comprehension failure on these sentences, regardless of the size and extent of their lesion (Fig. 1). Granted, our task demanded more from patients than mere comprehension, given the memory delay involved. However, all patients performed well above chance on all irreversible sentence conditions, suggesting that low-level deficits in lexical processing and short-term memory could not explain their sentence comprehension problems. Rather, it seems that understanding “who did what to whom” in RSO sentences places high demands on cognitive systems that are likely to be impaired by any lesion that causes significant aphasia. Our studies in controls (Meltzer & Braun, 2011; Meltzer et al., 2010), like many other studies (Cooke et al., 2002; Newman, Ikuta, & Burns, 2010; Stromswold, Caplan, Alpert, & Rauch, 1996), have shown that RSO sentences induce increased neural activity in language relevant areas, particularly left IFG. In the current studies, patients showed virtually no evidence of increased activity for these sentences relative to the RSS condition. This suggests that aphasic patients do not engage in extra (unsuccessful) effort to parse sentences that exceed their comprehension abilities. Rather, they seem to apply the same amount of neural processing to complex sentences as they do to syntactically simpler sentences, which is not sufficient to obtain the correct interpretation.

Nonetheless, patients do exhibit increased neural activity for specific sentence conditions that are more challenging but still understood. Sentences that are reversible but not necessarily complex have recently received more scrutiny in neurolinguistics, using both neuroimaging techniques (Richardson, Thomas, & Price, 2010; Schafer, Page, Arora, Sherwin, & Constable, 2012) and lesion studies (Levy et al., 2012). Although syntactically complex non-canonical sentences are especially interesting in theoretical linguistics, their relevance to everyday language comprehension is questionable, as they are relatively uncommon in ordinary use (Roland, Dick, & Elman, 2007). In contrast, semantic reversibility is a feature of many sentences. Comprehension of reversible sentences requires successful processing of syntactic cues (in English, chiefly word order) in order to determine “who did what to whom,” even if only the most basic syntactic structures are used. In this study, we found that some patients, despite having relatively mild expressive aphasia, were impaired on understanding even simple reversible sentences, such as “The boy is pushing the girl out of the way.” This deficit was highly correlated with other measures of comprehension, including the WAB auditory-verbal comprehension subscore and an offline sentence-picture matching task that did not involve an enforced memory delay. Therefore, even though the difficulties of reversible sentences may be exacerbated by the challenges of our task paradigm (including the memory delay and forced-choice response), performance on reversible non-complex sentences appears to be a reasonable indicator of overall language comprehension success as experienced in daily life by the participants.

Such general problems with thematic role comprehension in non-complex sentences have occasionally been reported in the literature (Davis et al., 2008; Miozzo, Fischer-Baum, & Postman, 2008). One VLSM study has reported an association between thematic role comprehension and damage to the lateral temporal lobe (Wu, Waller, & Chatterjee, 2007), while a later study instead reported effects in a more superior and posterior region in the temporo-parietal junction (Thothathiri, Kimberg, & Schwartz, 2012). Our present results are broadly consistent with these, as significant correlations were detected between comprehension performance and lesion extent, primarily in the middle temporal and angular gyri. Lesions in the frontal lobe did not appear to significantly impact comprehension of reversible non-complex sentences, although they did strongly affect language production measures (see Supplementary Information).

4.2. Compensatory neural activity measured with MEG

The high variability of patient performance in syntactic comprehension (the SynComp variable) offered not only the opportunity to assess the relationship between lesion location and comprehension with VLSM, but also to assess the role of compensatory neural activity in brain regions outside the lesion zone, using MEG to measure neuronal activation during task performance. MEG activation maps in healthy controls were concordant with VLSM results in that strong activation was observed in the lateral temporal lobe during the sentence presentation and memory delay stages, for comparisons of reversible vs. irreversible sentences. However, activation was also observed outside the temporal lobe, in frontal-parietal regions, but highly left-lateralized in all regions. In contrast, the activation maps observed in aphasic patients were more bilateral, with much more activity in the right hemisphere. We caution that these results do not mean that aphasic patients fail to activate the left hemisphere altogether, but their activation patterns in the left hemisphere were much more variable, due to their lesions, leading to weak statistical significance at the voxel level. For this reason, we supplemented our voxel-wise analysis of correlations with an ROI-based approach (Supplementary information, Fig S4), but it led to the same conclusion.

As discussed in the introduction, right-hemisphere activation in aphasic patients during language tasks is a common finding subject to differing interpretations. Due to the high variability present in our patients on understanding reversible sentences, the present dataset is ideal for evaluating the correlations between performance and activation on exactly the same task. The most definitive indication of activity related to adaptive recruitment, as opposed to maladaptive overactivation, is a correlation with performance. Given that our VLSM results showed that damage to the left temporal lobe is associated with comprehension impairment for reversible sentences, one might expect neural activity in the *right* temporal lobe to be correlated with better performance across the patients. We did not observe such a pattern. Although patients did exhibit significant activation in the right temporal lobe, it was not correlated with performance. Therefore, our data do not clarify the role of right temporal activation during language comprehension in aphasia: it may be adaptive or maladaptive.

Nonetheless, we did observe significant correlations between MEG activation and comprehension performance across the patients. These correlations were present in bilateral parietal cortex during sentence presentation, and in right parietal and frontal areas during the delay period. These right hemisphere regions are not significantly activated in control subjects. The MEG data therefore suggest that differential comprehension success in aphasic patients may be driven by recruitment of alternative cognitive strategies, rather than simply implementing language comprehension in the right hemisphere homologs of the “ordinary” perisylvian regions.

The suggestion that alternative cognitive strategies may underlie successful recovery outcomes is particularly encouraging, given that strategies may be explicitly trained and practiced during behavioral therapy. Further research will be necessary to elucidate the cognitive nature of alternative strategies adopted by recovered aphasic patients, but we can use the present results to speculate on what recovered patients may be doing to achieve better language comprehension. The task that we chose requires participants not only to process a sentence as it is heard, but also to retain the meaning during the three-second delay period and use this information to select the correct picture. Thus, short-term memory (STM) plays a critical role in this task, as it does in most language processing tasks. A growing body of data suggests that impairments to short-term and working memory may be the underlying cause of many of the linguistic deficits present in aphasia (Amici et al., 2007; Murray, 2012; Wright & Fergadiotis, 2012). However, efficient use of STM can also play a compensatory role in aphasia. Although language comprehension is usually a fairly

instantaneous and effortless process for healthy people, patients with aphasia may rely more on effortful “reprocessing” of language input in STM. If a sentence’s meaning is not understood right away, holding the sentence’s content in STM may provide a second chance to derive the correct meaning. Previous evidence for increased reliance on STM-based reanalysis in aphasic patients comes from studies showing improved comprehension of speech presented at slower rates (Nicholas & Brookshire, 1986; Pashek & Brookshire, 1982), and from studies showing that aphasic patients can display sensitivity to long-distance syntactic dependencies as healthy comprehenders do, but at greatly extended latencies (Burkhardt, Pinango, & Wong, 2003; Love, Swinney, Walenski, & Zurif, 2008).

Our imaging data are consistent with a shift from a relatively automatic mechanism of semantic comprehension to reliance on more extended reanalysis, dependent on general cognitive resources. Even though comprehension of reversible sentences was most adversely affected by lesions in the left middle temporal lobe, we did not see evidence of increased recruitment of the right temporal lobe in aphasics relative to controls, nor did activation there correlate with performance. Rather, better comprehension was correlated with neural activity in more dorsal portions of the right-hemisphere frontal and parietal lobes, particularly during the memory delay period. These areas are more typically activated in neuroimaging studies of working memory (Postle, 2006; Wager & Smith, 2003) but also in numerous other tasks involving high demands on general cognitive resources such as attention and executive function, such that they are now commonly referred to as the “task-positive network” (Fox et al., 2005). The putative functions of this frontal-parietal network include not only phonological rehearsal but also effortful updating and manipulation of items in short-term storage (Baddeley, 2003; Smith & Jonides, 1999; Veltman, Rombouts, & Dolan, 2003). Thus, patients who successfully compensate for left temporal lobe damage seem to recruit more general cognitive resources in an effortful process for determining the meaning of sentences. Successful sentence comprehension in aphasia is supported by reanalysis of sentences in verbal short-term memory, which may draw more heavily on right hemispheric networks in aphasic patients than in controls.

This finding suggests that ordinary language comprehension in aphasic patients may resemble the effortful language processing that healthy subjects must engage in under adverse task conditions. Behavioral studies have drawn parallels between aphasic patients and healthy adults dealing with degraded stimuli (Dick et al., 2001), and a recent PET study showed increased frontal-parietal connectivity both in aphasic patients relative to controls, and in controls listening to noise-degraded speech vs. speech alone (Sharp, Turkheimer, Bose, Scott, & Wise, 2010). Similarly, a recent fMRI study (Thompson, den Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010) showed that treatment-induced gains in comprehension performance were associated with a shift in activation from the left temporal lobe to bilateral inferior parietal regions, similar to those that correlated with performance during sentence perception in our patients. Our pattern of results demonstrates a continuum of effort required to process sentences of increasing difficulty. The easiest sentences (irreversible) are understood by patients, and elicit less neural activity. Reversible non-complex sentences elicit greater activity in both controls and patients throughout the perisylvian language networks, with better-performing patients showing more activity in dorsal parietal-frontal regions. The most difficult sentences, the reversible complex ones, elicit still greater activity in controls (particularly during the memory delay period), but not in aphasic patients. In this respect, patients understanding simple reversible sentences may resemble controls understanding complex sentences, employing a higher degree of effort for rehearsal and reanalysis to support comprehension.

We believe these findings are encouraging for the future development of interventions to improve language comprehension in aphasia. Much emphasis has been put on the potential

roles of contralateral homologous takeover and perilesional structural plasticity in aphasia recovery, but there are few tools at a therapist's disposal for influencing such processes. In contrast, a shift to effortful reprocessing using alternative cognitive strategies is exactly the kind of mechanism that behavioral therapy can teach explicitly. Some of the most promising treatments of comprehension disorders to date employ explicit strategy training to teach patients the grammatical mapping of sentence constituents to thematic roles (Schwartz, Saffran, Fink, Myers, & Martin, 1994; Thompson & Shapiro, 2005). Those treatments have largely emphasized comprehension of material of increasing syntactic complexity. The present results suggest that reversibility may be a more important factor in overall language comprehension abilities that impact a patient's quality of life. Even for syntactically simple sentences, explicit training on rehearsal and reanalysis of sentence structure may lead to increased recruitment of intact neural systems to support recovery of comprehension. Future studies with aphasic patients may explore this as an avenue of treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Task Design. (A) Schematic illustration of trial structure. On each trial, subjects heard a sentence while viewing a fixation cross. After a 3 s delay, two pictures appeared, the target and a foil. (B) Illustration of the placement of digital triggers within the sound files of individual sentences, to allow analysis of MEG data timelocked to specific points within and following the sentence. (C) A sample picture set for the reversible sentence “The woman who the man is teaching is very tired right now.” The target shows the correct arrangement. A syntactic foil has the thematic roles of the two named actors switched, while a lexical foil substitutes one of the actors. (D) A sample picture set for the irreversible sentence “The glass that the man is washing has a small chip in it.”

Fig. 2. Patient Comprehension Performance. (A) Average percent incorrect for each of 12 conditions, varying according to semantic reversibility (R=reversible, I=irreversible), syntactic structure (SS=subject-relative, SO=object-relative, AC=simple active), and foil type. The two conditions comprising the Syntactic Comprehension score "SynComp" are marked with the letters "SC." (B) Composite scores of individual patient on different conditions combined. The box plot shows the group median, interquartile range, and full range as well as each individual score.

Fig. 3.

Correlations between behavioral scores and lesion size. (A) SynComp vs. Aphasia Quotient from the Western Aphasia Battery, (B) SynComp vs. Auditory-verbal Comprehension subscore from the Western Aphasia Battery, (C) Percent of left cortex lesioned vs. Aphasia Quotient, and (D) Percent of left cortex lesioned vs. SynComp.

Fig. 4. Voxel-based Lesion Symptom Mapping Results. (A) Lesion overlap map showing distribution of lesions in the left hemisphere (not a VLSM result). Voxels colored orange to yellow had at least five lesions and were included in the VLSM tests. (B) VLSM results on the SynComp score. Positive values indicate that a lesion causes a decrement on performance. Thresholded at $p < 0.05$ at voxel and cluster-correction levels. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

Fig. 5.

MEG maps for specific activity, reversible minus irreversible sentences. (A) Activation in young healthy controls during the post-RC phase of sentence comprehension (left panel) and during the memory delay (right panel). The left-right panel convention for the two time windows applies to all parts of Fig. 4 and Supplementary Figs. S3, S5, and S6. Thresholded at $p < 0.01$ voxel-wise, $p < 0.05$ cluster-corrected. (B) Activation in aphasic patients. $p < 0.01$ voxel-wise, $p < 0.05$ cluster-corrected. (C) Subtraction map comparing aphasic patients vs. young controls. $p < 0.025$ voxel-wise, $p < 0.05$ cluster-corrected. (D) Correlation (Spearman's Rho) between MEG specific activity and the Syntactic Comprehension score in the patient group. $p < 0.025$ voxel-wise, $p < 0.05$ cluster-corrected.

Table 1

Characteristics of individual participants.

Subject number	Age	Years of Education	Years post-stroke	Sex	% of left cortex damaged	Repetition composite	Lexical receptive composite	lexical expressive composite	PAL sentence picture matching	WAB: AVC	WAB: AQ	SLP diagnosis
						100	100	100	40	200	100	MAX SCORES
1	71	18	7.3	F	19	68	98	87	35	183	79	mild-moderate anomic aphasia
2	44	17	5.3	M	17	67	95	92	36	196	87	mild-moderate anomic aphasia
3	51	13	5.1	F	16	65	94	96	36	187	85	mild nonfluent aphasia
4	53	13	0.7	M	1	92	93	95	28	180	92	mild to moderate fluent aphasia
5	59	16	10.0	M	1	97	98	97	37	200	94	mild anomic aphasia
6	69	17	3.0	F	10	81	91	86	29	180	82	moderate anomic aphasia
7	71	17	11.7	F	24	50	80	88	28	169	79	moderate anomic aphasia
8	61	12	5.9	M	13	95	95	92	38	177	92	mild anomic aphasia
9	67	17	24.3	F	15	65	95	96	37	182	89	mild conduction aphasia
10	39	17	9.3	M	23	60	97	98	28	193	93	mild anomic aphasia
11	64	18	9.6	M	12	99	94	91	35	182	88	mild anomic aphasia
12	49	15	1.3	F	0	98	94	94	32	193	96	mild anomic aphasia
13	48	12	1.4	M	11	95	94	93	31	190	90	mild anomic aphasia
14	47	17	2.0	F	23	79	93	96	27	175	90	mild anomic aphasia
15	50	17	2.9	M	8	80	88	98	32	182	83	mild anomic aphasia
16	56	20	1.7	M	7	88	97	95	38	166	93	mild-moderate anomic aphasia
17	40	17	1.7	M	21	76	82	86	28	145	73	moderate Broca's aphasia

Subject number	Age	Years of Education	Years post-stroke	Sex	% of left cortex damaged	Repetition composite	Lexical receptive composite	lexical expressive composite	PAL sentence picture matching	WAB: AVC	WAB: AQ	SLP diagnosis
18	62	14	2.3	F	6	86	87	84	27	161	85	moderate anomic aphasia
19	57	22	8.1	M	45	73	93	74	29	169	75	moderate Broca's aphasia
20	71	19	5.4	M	4	84	95	97	36	200	94	mild anomic aphasia
21	63	15	5.0	F	32	69	84	74	28	134	66	moderate Broca's aphasia
22	67	21	9.5	F	21	97	98	90	32	178	92	mild anomic aphasia
23	34	18	5.0	F	10	68	90	99	38	199	96	mild anomic aphasia
24	72	20	6.9	M	13	97	96	97	35	185	97	very mild anomic aphasia
25	57	19	5.2	M	3	95	97	93	34	179	89	mild anomic aphasia

Explanation of fields:

% of Left Cortex Damaged – Lesion masks defined on each participant were warped into Talairach space, and the overlap with a mask of Left Hemisphere Cortex was computed. Subjects #5 and #12 had subcortical infarcts, resulting in minimal cortical damage but substantial motor deficits.

Repetition Composite – Average percent score on the PALPA subtest 8 (repetition of nonwords of one, two, or three syllables) and the repetition subtest of the WAB, which includes words, phrases, and sentences.

Lexical Receptive Composite – Average percent score on the Auditory Word Recognition subtest of the WAB and three subtests of the PALPA (#5, Auditory Lexical Decision, #47, spoken picture matching, and #49, Auditory Synonym Judgment).

Lexical Expressive Composite – Average percent score on object naming from the WAB, and the Druks and Masterson Action and Object naming batteries.

PAL Sentence-Picture Matching – An offline test with 40 trials similar to the task performed by the patients during MEG experiment.

WAB AVC – Auditory Verbal Comprehension subscore from the Western Aphasia Battery.

WAB AQ– “Aphasia Quotient” from the Western Aphasia Battery, an overall measure of aphasia severity (lower score=worse aphasia).

SLP diagnosis – Type of aphasia determined by formal testing and clinical impression by a Speech Language Pathologist (author JR).

Table 2

Example sentences in six conditions. Slashes indicate prosodic boundaries, during which a brief pause occurred.

Code	Reversibility	Syntactic complexity	Example sentences
RSS	Reversible	Subject-embedded clause	The man/who is teaching the woman/ is discussing a hard problem The woman/who is teaching the man/ is very tired right now
RSO	Reversible	Object-embedded clause	The man/who the woman is teaching/is discussing a hard problem The woman/who the man is teaching/ is very tired right now
RAC	Reversible	Simple Active	The man/is teaching the woman/ about a hard math problem The woman/is teaching the man/ about a hard math problem
ISS	Irreversible	Subject-embedded clause	The man/who is washing the car/ is doing a sloppy job The woman/who is washing the glass/ is not using enough soap
ISO	Irreversible	Object-embedded clause	The glass/that the man is washing/ has a small chip in it The car/that the woman is washing/ has over 50,000 miles
IAC	Irreversible	Simple Active	The man/is washing the glass/ in the kitchen sink The woman/is washing the car/ on a Sunday afternoon

Table 3

Correlations between “SynComp” syntactic comprehension performance, and lesion extent in various regions of interest.

ROI name	ρ	p -value
Angular gyrus	-0.57	0.00271 *
IFG, pars opercularis	0.17	0.42
IFG, pars orbitalis	-0.06	0.78
IFG, pars triangularis	0.02	0.92
Inferior parietal lobe	-0.28	0.18
Middle frontal gyrus	0.17	0.42
Middle temporal gyrus	-0.72	0.00005 *
Precentral gyrus	0.16	0.43
Superior frontal gyrus	0.07	0.73
Supplementary motor area	-0.02	0.91
Superior medial gyrus	-0.06	0.78
Superior temporal gyrus	-0.38	0.06
Temporal pole	-0.31	0.13

IFG, inferior frontal gyrus.

* $p < .0038$ (Bonferroni correction of $p < .05$ for 13 comparisons)