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Neural plasticity and treatment-induced recovery of sentence processing in agrammatism

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Abstract

This study examined patterns of neural activation associated with treatment-induced improvement of complex sentence production (and comprehension) in six individuals with stroke-induced agrammatic aphasia, taking into account possible alterations in blood flow often associated with stroke, including delayed time-to-peak of the hemodynamic response function (HRF) and hypoperfused tissue. Aphasic participants performed an auditory verification fMRI task, processing object cleft, subject cleft, and simple active sentences, prior to and following a course of Treatment of Underlying Forms (TUF; Thompson et al., 2003), a linguistically based approach for treating aphasic sentence deficits, which targeted object relative clause constructions. The patients also were scanned in a long-trials task to examine HRFs, to account for any local deviations resulting from stroke, and perfusion images were obtained to evaluate regions of hypoperfused tissue. Region-of-interest (ROI) analyses were conducted (bilaterally), modeling participant-specific local HRFs in left hemisphere areas activated by 12 healthy age-matched volunteers performing the same task, including the middle and inferior frontal gyri, precentral gyrus, middle and superior temporal gyri, and insula, and additional regions associated with complex syntactic processing, including the posterior perisylvian and superior parietal cortices. Results showed that, despite individual variation in activation differences from pre- to post-treatment scans in the aphasic participants, main-effects analyses revealed a general shift from left superior temporal activation to more posterior temporoparietal areas, bilaterally. Time-to-peak of these responses correlated negatively with blood flow, as measured with perfusion imaging.

Keywords

agrammatic aphasia; fMRI; syntax; TUF; stroke; brain lesion

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Introduction

It is well known that individuals with aphasia resulting from stroke show recovery of language function despite damage to the neural network supporting language and that treatment aimed to improve language impairments boosts this recovery even in the chronic phase of stroke recovery (Holland, Fromm, DeRuyter, & Stein, 1996). However, the neural mechanisms underlying treatment-induced recovery are little understood and neuroimaging studies examining these effects have resulted in mixed findings (see for review: Crinion & Leff, 2007; Price & Crinion, 2005; Thompson & den Ouden, 2008). Some studies find recruitment of right hemisphere regions/networks, often involving tissue in areas homologous to left hemisphere language regions, particularly in patients with large lesions (Brier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007; Cherney & Small, 2006; Crosson et al., 2005; Raboyeau et al., 2008; Vitali et al., 2007). Others report treatment-induced recruitment of left hemisphere perilesional tissue, adjacent to damaged areas in the language network, which might be prone to subserve language due to functional redundancy (Davis, Harrington, & Baynes, 2006; Leger et al., 2002; Meinzer et al., 2008; Vitali et al., 2007). A third pattern finds activation of areas distal to the lesion, which are not normally engaged during language processing (e.g. Fridriksson, Morrow-Odom, Moser, Fridriksson, & Bayliss, 2006).

In the present study, we examined the neural mechanisms engaged to support recovery of sentence level deficits in patients with agrammatic aphasia. These patients often show deficits in both production and comprehension of complex, noncanonically ordered sentences, such as object relative constructions in English (Grodzinsky, 1990; Schwartz, Linebarger, Saffran, & Pate, 1987). Notably, few studies have examined how brain activity changes when sentence production and/or comprehension are improved (Cherney & Small, 2006; Thompson, Fix, Gitelman, Parrish, & Mesulam, 2000; Wierenga et al., 2006). Results of these studies are in keeping with the aforementioned general recovery patterns. That is, studies find post-treatment recruitment of right and/or left hemisphere regions. As pointed out by Thompson and den Ouden (2008), a number of factors may underlie the variable patterns of treatment-induced neural recruitment found in the literature. Patient variables, such as lesion site/extent and type/severity of specific aphasic symptoms, as well as study variables, such as the focus/type of the treatment and scanning tasks, impact patterns of neural plasticity in ways that are as yet unresolved and under investigation.

Other important factors that have not been considered in neuroimaging studies of recovery concern alterations in cerebral blood flow that accompany stroke in some patients. Bonakdarpour, Parrish, and Thompson (2007), for example, showed that in three of five patients with aphasia secondary to stroke, time-to-peak (TTP) of the BOLD hemodynamic response function (HRF) was delayed, particularly in left hemisphere perilesional regions. This delay resulted in underestimation or lack of detection of ongoing neural activity when a canonical HRF was used to model the functional MRI data of these patients. Thus, it is possible that some heterogeneity in neural recruitment patterns reported in the extant literature is a by-product of the methods used to detect the BOLD signal in fMRI studies with patients. Another issue involves the extent to which neural tissue is hypoperfused in regions of the brain either ipsilateral or contralateral to the lesion. Indeed, few studies provide detailed structural lesion data and even fewer have considered patterns of hypoperfused tissue, which may preclude functioning in some areas of the brain even in chronic phases of recovery (Love, Swinney, Wong, & Buxton, 2002). Hillis and colleagues (e.g., Hillis, Barker, Beauchamp, Gordon, & Wityk, 2000; Hillis et al., 2006) have shown that perilesional hypoperfused tissue is common in acute stroke and that reperfusion of this tissue through intervention is highly correlated with improvement on language tasks.

However, the relation between hypoperfused tissue and language recovery has not been studied in chronic aphasia.

The training method investigated in the present study is Treatment of Underlying-Forms (TUF), a linguistically based method shown to be effective for improving sentence production and comprehension in agrammatic aphasia (Ballard & Thompson, 1999; Jacobs & Thompson, 2000; Thompson, Ballard, & Shapiro, 1998; Thompson, Choy, Holland, & Cole, 2010; Thompson, et al., 1997; Thompson, Shapiro, Kiran, & Sobecks, 2003). Participants were trained to produce and comprehend syntactically complex sentences, while generalization was tested to less complex constructions. Based on the Complexity Account of Treatment Efficacy (CATE: Thompson et al., 2003) as well as the results of previous studies (see Thompson & Shapiro, 2007, for review), we predicted improvements on both trained and untrained forms.

Neuroimaging studies with healthy listeners have shown that processing complex sentences with syntactic dependencies engages a left hemisphere network, including both anterior (inferior frontal gyrus) and posterior (superior and middle temporal gyri) tissue (Ben-Shachar, Hendler, Kahn, Ben-Bashat, & Grodzinsky, 2003; Caplan 2001; Caplan, Alpert, & Waters, 1998; Caplan et al., 2001; Cooke et al., 1999; Just, Carpenter, Keller, Eddy, & Thulborn, 1996; Röder, Stock, Neville, Bien, & Rösler, 2002; Santi & Grodzinsky, 2007; Stromswold, Caplan, Alpert, & Rauch, 1996). We hypothesized that spared tissue in these regions in either the undamaged or lesioned hemisphere would be likely candidates for the neural support of recovery. In order to compare activation patterns specific to the task and make predictions as to the involvement of potentially critical areas, we used activation patterns found in healthy controls to evaluate pre- to post-treatment changes in each aphasic participant.

Method

Participants

Six agrammatic aphasic speakers and 12 healthy age-matched volunteers participated in the study. All provided written informed consent prior to entry into the study and they were compensated for their participation. The study was approved by the Institutional Review Board (IRB) at Northwestern University.

Healthy participants—Five male and seven female non-brain-damaged volunteers ranging in age from 32 to 79 years (M = 54) were recruited from the greater Chicago area. All were strongly right handed (based on scores derived from the Edinburgh Handedness Inventory; Oldfield, 1971), monolingual, native speakers of English, and were without history of neurological, speech, language or learning problems. The mean number of years of education was 17.3 (range 15–20). All participants passed a hearing screening at 500, 1000, 2000, and 4000 Hz at 30 dB in both ears and had normal or corrected-to-normal vision (self-reported).

Agrammatic aphasic participants—The aphasic participants included 5 males and 1 female, age-matched with the healthy participants (range = 38–66 years; M = 54). All presented with aphasia secondary to a single left hemisphere stroke involving the middle cerebral artery (MCA), with the exception of one participant (A1) who had a crossed aphasia with a right hemisphere lesion (see Fig. 1 and Table 1 for lesion information for all participants). Participants were between 6 and 146 months post stroke at the time of the study. Years of education ranged from 12 to 20 and all were employed at the time of their stroke, apart from A5, who was close to obtaining his degree from medical school (see Table 2). The Western Aphasia Battery (WAB; Kertesz, 1982) and the Northwestern Assessment

of Verbs and Sentences (NAVS; Thompson, experimental version) were administered to all participants. In addition, narrative language samples were collected by asking participants to tell the story of Cinderella after viewing a picture book of the story. These samples were analyzed for a variety of linguistic variables, viz. mean length of utterance (MLU), percentage of grammatical sentences, the ratio of open to closed class words, ratio of noun to verb production, and percentage of verbs used with correct arguments (after Thompson et al., 1995). A reading test designed to include the words and sentence types used in the study also was administered, which all participants passed. All participants also passed screenings for more than mild dysarthria and/or apraxia of speech.

Results derived from the WAB, NAVS, and narrative language samples are shown in Table 3. WAB Aphasia Quotients (AQs) ranged from 66.8 to 85, indicating aphasia in the mild to moderate severity range. For all participants, production was more impaired than comprehension. Spontaneous speech was characterized by reduced phrase length (MLU ranged from 4.78 to 7.61), grammatical sentences (the percent of grammatical sentences produced ranged from 29% to 73%), and use of closed class words (mean open:closed class ratio = 1.78). In addition, the patients showed better production of nouns as compared to verbs (mean noun:verb ratio = 1.65). Performance on the NAVS also showed better sentence comprehension than production, but all participants showed superior performance in both modalities for canonical (subject-verb-object (S-V-O), in English) compared to noncanonical structures. None of the participants were able to produce object relative (OR) structures prior to treatment.

Treatment procedures

Sentence structures and stimuli—Participants were trained to produce object relative (OR) sentences, as in 1a, using TUF (see Thompson 2008, for details). Throughout treatment, generalization was tested to untrained object cleft (OC) structures as in 1b and object extracted wh-questions (OWH) as in 1c.

1. a. Pete saw the groom that the bride carried _____. (OR)

b. It was the groom that the bride carried _____. (OC)

c. Who did the bride carry _____? (OWH)

Based on derivational syntax, these structures are linguistically similar in that all involve Wh-movement of a wh-element (i.e., who, that) from a position following the verb (marked by blank spaces in the examples above) to a position earlier in the sentence. This movement introduces a level of complexity that is not inherent in, for example, simple active sentences. However, among the sentences, 1a is more complex than 1b (due to the additional presence of subject raising in 1a, but not in 1b), which is more complex than 1c (because 1b, but not 1c, involves clause embedding) (Chomsky, 1977, 1981, 1995; Cheng & Corver, 2006; also see Thompson & Shapiro, 2007). Notably, previous treatment research has shown that training 1a improves production and comprehension of all three sentence types (Thompson et al., 2003; Thompson et al., 2010).

Ten active sentences with semantically reversible participant roles were developed (i.e., *The groom carried the bride*) and for each sentence two corresponding black and white line-drawn pictures were prepared (e.g., a groom carrying a bride and a bride carrying a groom), for a total of 20 picture stimuli. All sentences contained transitive verbs, controlled for length, frequency, and other variables known to influence lexical processing and production.

Experimental design—A modified multiple baseline design across participants, combined with a multiple probe technique, was used to evaluate the effects of treatment

(Thompson, 2006). Prior to treatment, two baseline probes, which tested both comprehension and production of all sentence types, were administered (see below). For participants A2, A4, and A6 these probes were administered on two separate days during week 1 of the study, following which treatment was begun during week 2. For Participants A1, A3, and A5, baseline probes were extended across 4 weeks, with treatment commencing during week 5, with the longer baseline period for the latter subjects serving as experimental control (see Fig. 2).

Following baseline testing, treatment was begun, with participants seen for two 2-h sessions per week. During each session, the 20 OR items were trained in random order. Daily, prior to each training session, probes identical to those used for baseline testing were administered so that acquisition of OR structures and generalization to OC and OWH structures could be observed. A randomly selected half of the items were administered each day (30 production and 30 comprehension items), resulting in a full probe weekly. For each participant, treatment was provided until 80% correct OR production was achieved on two successive probes or for a maximum of 20 sessions. For a subset of production and comprehension probes (15%), responses were scored by two independent raters, revealing 99.1% inter-rater reliability for production probes and 100% reliability for comprehension probes. After treatment was completed, the NAVS was readministered.

Comprehension and production probe tasks—The 20 picture stimuli were presented three times each, once for elicitation of each sentence type, for a total of 60 comprehension and 60 production items. Probes were computer generated using Superlab Pro (version 2.0.4; http://www.cedrus.com), such that the probe tasks would be as similar as possible to the task used in our fMRI conditions (see below).

Comprehension probes used a sentence picture matching task: presented with picture pairs on the computer screen. Participants were instructed to “point to the picture that goes with the sentence”, which was then auditorily presented by a pre-recorded female voice. A 5-s response time was provided, after which the computer advanced to the next item. For production, a sentence production priming procedure was used: a picture pair appeared on the computer screen and a pre-recorded female voice modeled the target sentence type using the picture on the left side of the screen as it was highlighted (“*For this picture, I could say: <example sentence>*”). Instruction to make a similar sentence for the target picture was then given as the picture on the right side of the screen was highlighted (“*For this picture, YOU could say: …*”). A maximum of 10 s was provided for responding, after which the computer proceeded to the next item. Responses were considered correct if the target sentence type was produced with a verb and both the agent and theme arguments were represented. Semantically appropriate noun and verb substitutions were accepted (e.g., *man* for *boy*), but only substituted verbs with the same number and type of arguments engendered by the target verb were accepted (e.g., *chase* for *follow*). Functional category errors (e.g., verb tense substitution/omission, omission of determiners) also were accepted, but overt production of *that* (or *who*) was required for correct object relative and object cleft structures. That is, reduced relative clauses, such as *Pete saw the groom the bride carried.*, were not accepted even though they are grammatically correct.

Treatment data analysis—The primary dependent variable, reflecting responsiveness to treatment, was the proportion of correct OR responses noted on production and comprehension of probes. Generalization to untrained sentence types was a secondary variable of interest. Results of the study were examined, primarily, on an individual basis, in keeping with single-subject experimental design conventions. In addition to visual inspection of learning and generalization curves, effect sizes for the production probes were calculated for each participant, for each sentence type, using Busk & Serlin’s (1992)

variation on Cohen's *d* statistic (Cohen, 1988), as advocated by Beeson and Robey (2006). We subtracted the mean of the first three probes, which included the two baseline probes, from the mean of the two final probe scores and divided the result by the standard deviation of the first three probe scores. When the first three probes all yielded scores of 0, and thus no variation, we used the standard deviation of the respective participant's pooled baseline scores for the other two sentence types. With respect to interpretation of effect-size magnitude, we compared *d* values to the effect sizes reported by Robey, Schultz, Crawford, and Sinner (1999), based on their review of treatment research in aphasia: 2.6 (small), 3.9 (medium) and 5.8 (large).

We also evaluated treatment effects by computing performance change for all sentence types between baseline probe 1 and probe 2 for participants A1, A3, and A5 and comparing that to performance change for Participants A2, A4, and A6 from baseline probe 2 to the final treatment probe for production and comprehension, using independent-samples Mann-Whitney *U* tests. NAVS performance from pre- to post-treatment also was analyzed non-parametrically for the group using a Wilcoxon signed ranks test.

Functional imaging procedures

Primary neuroimaging task—An auditory verification task was selected to obtain the functional neuroimaging data. Participants, presented with an auditory sentence and a visual scene, indicated by button-press (yes/no) whether or not the two matched (see Fig. 3). Sentence types were object clefts (OC), which involve Wh-movement, subject clefts (SC), which are not derived through Wh-movement and have a canonical word order, and simple past tense actives (ACT), matched for sentence length in syllables (see 2a–2c). Half of the sentences presented in each condition matched the pictures, while the other half consisted of role-reversed mismatches. Sixty trials per condition were pseudorandomly distributed over 4 runs, in an event-related design. Picture stimuli remained on screen for 8000 ms, with ISI jittered between 300 and 22,000 ms, based on optimal design calculations using a customized version of OPTSEQ (http://surfer.nmr.mgh.harvard.edu/optseq/).

2. a. It was the groom that the bride carried. (OC)

b. It was the bride that carried the groom. (SC)

c. Yesterday, the bride carried the groom. (ACT)

Healthy control participants were scanned once, whereas pre-post treatment scans were obtained for the aphasic participants. With the exception of aphasic participant A1, who had a left-sided hemiparesis, all subjects used their left hand for the button-press response.

FMRI data acquisition and preprocessing—Scanning was carried out on a Siemens 3T TIM Trio scanner. A T1-weighted anatomical scan was obtained at the start of each protocol with the following parameters: TR = 2300 ms; TE = 3.36 ms; flip angle = 9°; image matrix = 224 × 256; FOV = 256; voxel size = 1 mm × 1 mm × 1 mm. During the experimental runs, functional volumes with BOLD contrast were obtained using gradient echo-planar imaging sequences (TR = 2000 ms; TE = 30 ms; flip angle = 80°; matrix size = 64 × 64; FOV = 220 mm; voxel size = 3.44 mm × 3.44 mm × 3 mm; 32 slices). To allow for image saturation, the first 6 volumes of each experimental run were discarded.

Data preprocessing and statistical analysis was performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Functional scans were corrected for slice-acquisition timing and realigned to a mean functional volume, with which the anatomical volume was then coregistered. Spatial normalization of the anatomical image to the Montreal Neurological Institute (MNI) 152-subject template brain (ICBM, NIH P-20 project) took

place through 'unified normalization' in SPM5, which combines segmentation, bias correction and spatial normalization in one model (Crinion et al., 2007). For the lesioned brains, medium regularization was used, whereas non-lesioned brains where normalized with light regularization. Functional volumes were then normalized using transformation parameters obtained from normalization of the coregistered T1s, and resliced at a resolution of 3 mm × 3 mm × 3 mm. Spatial smoothing was performed with a 6 mm (full-width, half-maximum) isotropic Gaussian kernel. Effects of global signal were removed from the functional time-series using the method described by Macey, Macey, Kumar, and Harper (2004). In the aphasic participants' data, signal intensity was scaled to allow comparison of pre- and post-treatment scans.

Long-trials task—The aphasic individuals also participated in a long-trials fMRI task, which was the same as the experimental task, but used a fixed SOA of 30 s and only 40 trials. We included this task to examine participant-specific hemodynamic response functions (HRFs), which are known to be delayed in some patients with stroke-induced aphasia and can, therefore, influence detection of fMRI activation in some regions of the brain (Bonakdarpour et al., 2007).

Perfusion imaging—For identification of hypoperfused tissue, which might affect cortical activation levels as reflected by the BOLD response, the aphasic participants underwent perfusion imaging by arterial spin labeling (ASL) with a modified PICORE/Q2TIPS sequence (Chen, 2008; Luh, Wong, Bandettini, & Hyde, 1999; Wong, Buxton, & Frank, 1997). Pulse sequence parameters were TI1 = 600 ms and TI2 = 1600 ms. Twenty Pairs of interleaved control and tag images were collected (TR = 2500 ms, TE = 2300 ms (minimum), slice thickness = 5 mm, with 1 mm gap; inplane resolution 3.44 mm × 3.44 mm). Resting state images were acquired using 50 averages.

Flow images were calculated from the interleaved control and tag time series using a surround subtraction method and averaged over the entire scan to provide an adequate signal-to-noise ratio (Chen, 2008; Wong et al., 1997). Results were quantified in ml/100 g/min and the images were then coregistered to the anatomical images and spatially normalized, using nearest neighbor interpolation for strict maintenance of flow values. Using each participant's normalized grey matter mask that formed the output of the T1 segmentation process in SPM5, we calculated the mean flow value for the grey matter in each ROI. We also calculated the mean flow value per hemisphere, again using the grey matter mask.

Correlations between perfusion and region-specific time-to-peak of the HRF were calculated using a Pearson test. In addition, relations between region-specific upregulation of fMRI activation after treatment (i.e., regions showing greater post- compared to pre-treatment activation) and perfusion and time-to-peak also were examined with independent-samples *t*-tests, dividing ROIs into two groups, viz. those that showed upregulation of activation after treatment and those that did not. The same analyses were performed using downregulation (i.e., regions showing lesser activation post-treatment) as the grouping factor and using 'differential activation' (up- or downregulation versus no change) as the grouping factor.

Control participants' fMRI data analysis—In the first-level analysis, a high-pass filter of 256 s was used to eliminate scanner drift. Response times and accuracy were modeled parametrically for each trial, to covary out their effects on the main conditions of interest. Individual participants' summary activation maps for main effects were entered into a second-level within-subjects 2 × 3 analysis of variance (ANOVA) with sentence-picture matching (2 levels) and sentence type (3 levels) as variables. All second-level statistics were evaluated at a voxelwise significance threshold of $p<.05$, corrected for multiple comparisons

per false discovery rate (FDR: Benjamini & Hochberg, 1995; Genovese, Lazar, & Nichols, 2002). A minimum cluster size threshold of 3 contiguous voxels (81 mm^3) was used.

Aphasic participants' fMRI data analysis—The fMRI data of our aphasic participants were analyzed individually to avoid problems associated with small sample sizes and grouping data from patients with heterogeneous lesions (Price, Crinion, & Friston, 2006). Within-session and between-session effects were computed and estimated in one fixed-effects model for each aphasic participant, with the four runs within each session modeled as separate regressors. As Smith et al. (2005) point out, drawing conclusions about longitudinally differential activation based solely on visual comparison of thresholded activation maps or on counts of total numbers of activated voxels has considerable drawbacks. Session-specific levels of baseline intensity affect which activated voxels 'survive' a particular threshold. This may result in Type I errors, in that the illusion of differences between sessions is created, while these differences may not be statistically significant when directly compared in terms of normalized activation strength.

We performed ROI analyses using participant-specific HRF functions, derived from analysis of the long-trials fMRI task, to examine activation in regions of significant activation in the control group (see below): Brodmann's Areas 7, 9, 13, 21, 22, 39, 40, 44, 45, bilaterally. The participants' true HRF in spared tissue was calculated in these 18 regions of interest, using Brain Voyager software (QX 1.4, Maastricht, The Netherlands). HRF latency maps were formed using linear correlation lag analysis of the stimulation onsets and the time series on a voxel by voxel basis. The map was thresholded at $r = .11–.20$, depending on signal to noise. Within a suprathresholded region of interest, a stimulus-locked average formed the HRF curve for that particular cluster (see Bonakdarpour et al., 2007, for further details). The obtained hemodynamic response patterns were fed as weights to the relevant FIR-modeled post-event time bins in the statistical model. Specific contrasts were calculated by giving positive and negative values to these weights, thus allowing *t*-tests to compare the different conditions. Brodmann's Area ROIs were based on the WFU-Pickatlas toolbox, version 2.0 (Maldjian, Laurienti, Kraft, & Burdette, 2003).

Results

Response to treatment

Fig. 4 shows the time course of improved production of both trained (OR) and untrained (OC and OWH) structures for the six agrammatic participants. Participants who received treatment immediately following baseline are shown on the left (A2, A4, A6), whereas those with extended baseline periods (A1, A3, and A5) are shown on the right. As can be seen, following stable baseline performance, Participants A2, A4, and A6 showed increases in the percent correct production of trained OR structures when treatment was applied, while performance on target structures remained low and stable for Participants A1, A3, and A5 during this period. Similarly, when treatment was provided for participants A1, A3, and A5, acquisition of OR structures improved. Effect size analyses (see Table 4) based on the OR production probe data showed medium effect sizes for A2, A3, A4, and A5 and a small effect size for A1. Note that A6 did not show acquisition of OR structures using the computerized probes task, despite his showing improvement during treatment sessions. We, therefore, commenced testing him with manual probes after eight treatment sessions, which showed an acquisition effect. Because the number of manual probe data points was not sufficient for calculation of effect size, we compared his combined baseline scores to his final probe scores using Chi^2, which was significant ($p<.001$).

Four of six participants also showed generalization to the (untrained) OC constructions, showing small (A3), medium (A2 and A5), and large (A4) effect sizes. In addition, four

participants showed medium (A3) to large (A2, A5, and A6) effect sizes for (untrained) OWH structures. A1 and A5 produced OWH structures at high levels prior to treatment, thus precluding generalization to these structures. Finally, statistical analysis of changes for all three sentence types from baseline probe 1 to probe 2 for participants A1, A3, and A5 were compared to changes from baseline probe 2 to the final probe for participants A2, A4, and A6, with independent-samples Mann-Whitney *U* tests for production and comprehension separately, which revealed significant treatment effects for production ($p = .004$), as well as for comprehension ($p = .035$).

The comprehension data for trained and untrained structures are shown in Fig. 5. As can be seen, baseline comprehension levels varied across participants with both A1 and A6 starting out with generally high scores. Because of this we did not calculate treatment effect sizes for these data. Notably, however, following training, comprehension levels for all structures was stable with scores over 80% correct for all participants, except for subject A3, whose comprehension scores for OWH structures remained variable throughout the treatment phase.

Scores on the NAVS from pre- to post-treatment for each participant are shown in Table 5. A Wilcoxon signed ranks test comparing pre-post scores for the group on NAVS production (SPPT) and comprehension (SCT) scores indicated that production increased significantly from 42% to 60% correct ($p<.05$), whereas the general increase in comprehension from a mean of 76% to 80% correct was not significant ($p = .12$).

Control participants' fMRI results

Behavioral Data—Repeated measures ANOVAs of scan task performance showed main effects of sentence type for both reaction time ($F(1.1,11.8) = 14.45$, $p<.05$) and accuracy ($F(1.2,13.7) = 8.85$, $p<.05$). Bonferroni corrected post-hoc testing revealed reaction times for SC sentences ($M = 2641$ ms) to be significantly faster than for OC and ACT sentences ($M = 3101$ and $M = 2861$ ms, respectively). With respect to accuracy, OC sentences yielded more erroneous responses ($M = 96\%$ correct) than SC and ACT sentences (both at $M = 99\%$ correct). There was also a significant correlation between reaction time and accuracy, with accurate responses being faster than inaccurate responses (Pearson $r(34) = -.47$, $p<.01$).

FMRI Activation Patterns—Factorial analysis of the healthy control participants' neuroimaging data revealed significant main effects of sentence type and trial type (i.e., matched versus no-match), but no interaction. The main effect of trial type was present in a small cluster (108 mm^3) in the left-hemisphere lingual gyrus and a slightly larger cluster (324 mm^3) in the left posterior insula. Further investigation of this effect, by comparing matched versus mismatched trials in directional *t*-tests, revealed that the effect in the left insula was carried by the contrast matched>mismatched. The lingual gyrus effect was not significant when measured with directional *t*-tests. The absence of an interaction between trial type and sentence type, as well as the minimal trial type effect, prompted us to collapse the matched and mismatched trials in further analyses of sentence type effects to increase power.

Analysis of sentence-type effects revealed a main effect of sentence type, driven by the contrast of OC>SC, which showed activated clusters in a large left-lateralized network, including the middle and inferior frontal gyri, precentral gyrus, anterior middle and superior temporal gyri, angular gyrus and anterior insula (see Table 6 and Fig. 6). In all clusters, data plotting revealed that the effects were driven by increases over baseline signal level for the OC condition, as opposed to decreases for the SC condition. A similar network was found when subject-cleft and simple active sentences were collapsed and compared to OC structures (OC>(SC + ACT)) (which contrasted sentences with Wh-movement to those

without Wh-movement), with the addition of left caudate (head) and bilateral thalamic activation. The contrast SC>OC revealed a small cluster of activation in the left posterior insula, which turned out to be driven by a decrease in the BOLD response for OC trials, relative to the baseline signal level (as determined visually by plotting responses in the activated cluster). No other contrasts showed significant activation.

Aphasic participants' fMRI results

Behavioral Data—Table 7 shows scan task accuracy and reaction time data for the aphasic participants. With regard to accuracy, four participants showed improved performance from pre- to post-treatment scans across sentence type: A1, A2, A3 and A6. However, when subjected to statistical analysis (Chi^2 (α = .05)), significant effects were found only for Participant A6 (for all three sentence types) and Participant 5 (for object clefts only). A Pearson analysis of the correlation between changes in accuracy and changes in response time revealed no correlation ($r(16) = .09$, $p = .7$).

The Reaction time data were analyzed with subject-specific 3 × 2 ANOVAs, with the factors sentence type (SC, OC, ACT) and time (pre, post). We only report significant main effects and interactions here, with main effects of sentence type tested post hoc with Bonferroni correction (α = .05). Participants A1, A2, and A5 showed significantly slower RTs post treatment (A1: $F(1,354) = 27.28$, $p<.05$, A2: $F(1,354) = 13.08$, $p<.05$, A5: $F(1,354) = 8.74$, $p<.05$) as compared to pre-treatment, as well as main effects of sentence type (A1: $F(2,354) = 12.08$, $p<.05$, A2: $F(2,354) = 5.94$, $p<.05$, A5: $F(2,354) = 5.60$, $p<.05$), reflecting slower RTs for OCs compared to the other sentence types. Conversely, participants A3 and A4 showed significantly faster RTs post treatment (A3: $F(1,354) = 8.57$, $p<.05$; A4: $F(1,344) = 10.16$, $p<.05$) and a main effect of sentence type was found for A3 ($F(2,354) = 4.33$, $p<.05$). In keeping with the other participants, this latter effect derived from longer RTs for OC compared to SC sentences. Participant A6 did not show a significant main effect for sentence type ($F(2,351) = 2.91$, $p = .056$).

Long-trials (HRF) and perfusion imaging results—Results of the whole-brain perfusion imaging analyses are graphically presented in Fig. 7, with region-specific blood flow values given in Table 8. Table 8 also shows the aphasic participants' time-to-peak (TTP) of the HRF in each ROI, based on the long-trials data. TTP cells are empty if no fluctuating HRF correlated with trial onset was observed in a particular region, usually due to lack of sufficient sparing of functional grey matter. The hemispheric asymmetries shown in Table 8 and the pattern visible in Fig. 7 indicate that perfusion was generally lower in the hemisphere directly affected by the stroke, with all participants showing higher perfusion in the contralesional hemisphere (i.e., in the right hemisphere for A2–A6 and the left hemisphere for A1, whose stroke affected the right hemisphere). Relatively low perfusion also extended beyond the immediate perilesional areas.

Correlational analysis examining the relation between blood flow values (i.e., perfusion) and TTP revealed a significant negative correlation (Pearson $r(103) = -.20$, $p<.05$). That is, lower perfusion was correlated with longer TTP for the hemodynamic response associated with neural activation (see Fig. 8). In addition, independent samples *t*-tests revealed significantly shorter TTPs ($t(101.9) = -4.793$, $p<.001$)) and higher perfusion levels ($t(106) = 2.089$, $p<.05$)) in regions showing post-treatment upregulation of activation (see below) compared to regions that did not (see Fig. 9). Conversely, there were no differences between regions showing or not showing downregulation for either TTP or perfusion levels. Finally, regions with pre-post changes in activation in either direction showed shorter TTPs than regions that showed no change ($t(91.0) = 3.024$, $p< 0.05$), and there were no differences in perfusion levels across these regions.

FMRI Activation Patterns—Analyses of the aphasic participants' pre- versus post-treatment fMRI data examined several ROIs, including frontal regions (BA 44, 45 and 9), the insula (BA 13), and temporoparietal areas (BA 21, 22, 39, 40, and 7). As noted above, these regions were selected because of their role in language processing noted in the literature and also based on the network identified for processing complex sentences in our healthy control participants. Because we anticipated tissue recruitment both ipsilateral and contralateral to the lesion, we examined for activation in these ROIs bilaterally. We report main-effect differences between the pre- and post-treatment scans, collapsing the three sentence types (although sentence types were separately modeled).

The aphasic participants with significant activation differences in the targeted ROIs for pre-treatment>post-treatment (pre>post) and post-treatment>pre-treatment (post>pre) contrasts are shown in Table 9. Fig. 10 also graphically displays these data, depicting the proportion of participants showing differential pre/post activation for main effects within each ROI. Note that some participants show both up- and downregulation within the same ROI, reflecting activation shifts within a particular region. Finally, in Fig. 11 we present cortical and axial maps for individual aphasic participants showing pre>post (blue) and post>pre (red) activation differences projected onto their skull-stripped and normalized brains.

Despite individual variation across patients, some common changes in activation were noted from pre- to post-treatment. In particular, in the left hemisphere, downregulation (that is, less activation post- as compared to pre-treatment) stood out in the insula (BA 13) and the superior temporal gyrus (BA 22), with minor downregulation in the triangular part of the inferior frontal gyrus (BA 45), while upregulation (that is, greater activation post- as compared to pre-treatment) was prominent in the middle temporal and angular gyri (BAs 21 and 39), as well as in superior parietal cortex (BA 7), with minor upregulation in the opercular part of the inferior frontal gyrus (BA 44). Pre to post-treatment changes were also noted in the right hemisphere: there was somewhat more downregulation than upregulation in the insula (BA 13) and the middle temporal gyrus (BA 21) and concomitant minor upregulation in frontal and prefrontal regions (BAs 44 and 9), with more prominent upregulation, compared to downregulation, in the supramarginal gyrus (BA 40) and superior parietal cortex (BA 7). The left supramarginal gyrus (BA 40) and prefrontal cortex (BA 9) and the right insula (BA 13), showed mixed patterns of both up- and downregulation, in some cases driven by activation shifts within the same regions by individual subjects, particularly patients A2 and A4.

The most consistent activation shifts from pre- to post-treatment noted in the main effects analysis for the patients showed up in the left angular gyrus (BA 39) and the superior parietal region bilaterally (BA 7). Only one patient (A4) showed pre>post activation in BA 39, whereas four of the five participants showed post>pre activation in this region (the lesion of A6 encompassed all of the angular gyrus). As for superior parietal area activation, A4 again showed bilateral pre>post activation, whereas A1, A2, and A4 showed post>pre activation in the left BA 7 and A1, A2, A4, and A6 showed post>pre activation in the right BA 7.

Discussion

Results of the present study replicated previous reports of the behavioral effects of TUF (Ballard & Thompson, 1999; Jacobs & Thompson, 2000; Thompson et al., 2010; Thompson et al., 1997; Thompson et al., 1998; Thompson et al., 2003). All participants, who showed inability to produce OC constructions prior to treatment, improved when treatment was provided. This translated to medium effect sizes for all participants, except A1 who showed a small effect size due to a decrease in performance accuracy on the final treatment probe.

All participants also showed improved sentence comprehension by the end of treatment, except A1 and A6, who showed good ability to comprehend both trained and untrained structures during baseline probing. Generalized production (and to some extent comprehension, when baseline ceiling effects did not preclude this) also was noted to less complex Wh-movement structures (i.e., OC and OWH) across participants, although effect sizes were variable because production of these structures was also variable during baseline for some participants for OCs (A1) and/or for OWHs (A1, A3, A5). The only exception to the pattern of overall generalization was participant A6, who showed no improvement on OC structures on the production probe task. Nevertheless, improved NAVS scores were noted following treatment, for both production and comprehension, which were statistically significant for sentence production for the group.

In order to interpret the neuroimaging data associated with this improvement, we used the data derived from our healthy volunteers as a guide. First of all, scan task performance by the healthy controls showed that the task was not trivial even for persons without impairment in syntactic processing, though the general error rate was low (2.1%). Participants took significantly less time to respond to SC sentences compared to OC sentences (though they also took longer to respond to simple active sentences, which may have reflected time required to process the temporal adverbs used in the simple active sentences), and they made significantly more errors in response to OC sentences than on the other two simpler sentence types. Thus, the OC sentence condition, arguably, placed greater cognitive demands on the syntactic processor than the other two sentence types. In the functional imaging data analysis, variations in response accuracy or RT were covaried out of the sentence-type-related variance at the first level of statistical analysis. However, correlation between these parameters and sentence type remind us that ‘difficulty’ of the task, or specific condition, is not easy to disentangle complexity, whether at the syntactic or other processing level.

Notably, the unimpaired participants showed a left-lateralized perisylvian network associated with complex syntactic processing, with increased activation associated with processing object cleft structures, as compared to subject cleft or active sentence structures. This network included both frontal (inferior and middle frontal gyri) and temporoparietal brain tissue (anterior middle temporal and superior temporal gyri and the angular gyrus), as well as the insula, similar to that found in previous neuroimaging studies of complex syntactic processing (Ben-Shachar et al., 2003; Caplan 2001; Caplan et al., 1998; Caplan, et al., 2001; Cooke et al., 1999; Crinion, Warburton, Lambon-Ralph, Howard, & Wise, 2006; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 1994; Humphries, Love, Swinney, & Hickok, 2005; Iijima, Fukui, & Sakai, 2009; Just et al., 1996; Mazoyer et al., 1993; Moro et al., 2001; Röder et al., 2002; Santi & Grodzinsky, 2007; Stowe et al., 1998; Stromswold et al., 1996).

Before discussing the functional imaging data in the aphasic participants, we point out that the observed correlation between decreased blood flow and increased hemodynamic response time-to-peak (TTP) as well as the relation between perfusion levels and propensity for upregulation of activity after training indicate the importance of taking into account participant-specific brain response parameters in brain imaging studies of clinical populations. The first finding is directly related to the nature of the BOLD response; it is unlikely that neural firing in an area with low perfusion effects a later *onset* of the hemodynamic response. Rather, the reduced level of blood flow means that it takes longer for a measurable surplus of oxyhemoglobin to arise, which is what is measured as a hemodynamic response peak in BOLD fMRI. The second finding confirms that locally reduced perfusion, certainly not limited to perilesional areas, but also extending into the contralateral hemisphere as observed in the present study, essentially extends the lesion in

patients with stroke, limiting the candidacy of affected regions for functional recovery. Importantly, hypoperfused tissue is not often associated with chronic stroke (though see Love et al., 2002). However, here we show that this phenomenon extends beyond the acute stage of stroke recovery. Further, the present results support Bonakdarpour et al. (2007) in that delayed TTP was seen in several ROIs in both hemispheres, indicating that functionality may be underestimated in analyses that limit the search space to a canonical hemodynamic response function based on healthy brain responses to neural activation.

With respect to changes in scan task performance in the aphasic participants from pre- to post-treatment, four patients showed improved accuracy on OC sentences, with variable performance on the other sentence types. For example, one patient showed improvement on all sentence types (A6), while another showed improvement on OC sentences only (A5). We are uncertain why accuracy in the scanner differed from that noted in treatment probes (which used a computer-generated task identical to that used in the scan task) or as measured by the NAVS. Indeed, all participants (except A5) showed comprehension at least at 80% correct on the final treatment probe for all sentence types (see Fig. 5) and, even A5 showed ability to correctly comprehend these sentences using paper probes. In addition, on the NAVS all participants showed good ability to comprehend subject cleft and active structures at pretesting, and above chance performance on object clefts was noted at post-testing. Therefore, it is likely that, despite responding incorrectly more so in, as compared to out of, the scanner, the patients were able to parse the sentences presented. Variation in RT from pre- to post treatment was also noted, with three patients responding more slowly post treatment, two patients being faster and one patient showing no change. Though these changes indicate that treatment affected task performance, their precise interpretation is not straightforward. Faster RTs following treatment suggest an improved facility to process complex sentences, however, longer RTs may just as well indicate a heightened awareness of and/or use of cognitive resources to carry out syntactic parsing as a result of treatment.

With regard to the fMRI data, what is noticeable for the agrammatic participants, at first glance, is individual variability in activation patterns, both for main effects and for pre-post treatment comparisons. This variability, apart from undoubtedly being related to the physical impact of stroke on healthy brains, may also reflect inherently different neural recruitment within individuals (see Caplan et al., 2007), likely attenuated by the impact of stroke. Given this possibility, nevertheless, our first scientific search remains for what the individuals have in common, i.e. what is shared between most individuals, in spite of their differences.

From this perspective, what stands out is a general shift in main-effects activation levels towards posterior perisylvian (LH, BA 39; RH, BA 40), superior parietal (bilateral, BA 7) and left-hemisphere middle temporal cortex (BA21), away from the left-hemisphere superior temporal gyrus (BA22) and the insula. Note that the angular gyrus only contained a small cluster of differential activation for the OC>SC contrast in healthy controls ($k = 3$), while supramarginal and superior parietal cortex did not show up in that contrast and were only added to our search space because of findings in the literature, which associated these regions with a possible role in syntactic processing. For example, these regions have been found to play a role in syntactic computations, such as verb argument structure processing (Den Ouden, Fix, Parrish, & Thompson, 2009; Thompson et al., 2007; Thompson, Bonakdarpour, & Fix, 2010). The pattern observed here, then, is suggestive of post-training upregulation in regions that are involved in ‘similar’ computations to those required for the parsing of complex syntactic sentences, or merely computations within the same domain (syntax). Inferior parietal, superior parietal, and prefrontal regions also have been reported to be a part of the network that supports verbal working memory (Tsukiura et al., 2001), which may mean that our subjects relied more heavily on verbal working memory in syntactic

parsing after training than they did before. At this stage, these interpretations of the observed shifts can only remain speculative.

Less prominent activation shifts were observed within the inferior frontal gyri (bilaterally), viz. from activation in the triangular part of the inferior frontal gyrus (BA 45) to the opercular part (BA 44). Both areas showed differential activation for the OC>SC contrast in our healthy controls. We do not wish to overemphasize this relatively minor shift, but we do point to literature that discusses possibly different roles for regions within the inferior frontal cortex, with BA 44 particularly claimed to play a crucial role in the computation of 'hierarchical dependencies' typical of complex syntactic structure (Bornkessel, Zysset, Friederici, von Cramon, & Schlesewsky, 2005; Bornkessel-Schlesewsky, Schlesewsky, & Cramon, 2009; Friedderici, et al., 2006a; Friederici, et al., 2006b; Stromswold et al., 1996), and the more anterior part of Broca's area supporting more lexically or semantically based processes (Friederici, Opitz & von Cramon, 2000; Bookheimer, 2002; Fiebach, Friederici, Muller, & von Cramon, 2002). In this light, our data would be consistent with a post-treatment return to recruitment of cortical tissue with the greatest potential to support complex syntactic processing.

Finally, returning to our earlier discussion regarding neural tissue recruited to support recovery, the present study indicates that left hemisphere tissue, not only perilesional, but also tissue some distance from the lesion has potential to become active for processing language following brain damage. The angular gyrus, for example, showed increased activation in the lesioned hemisphere following treatment, even for patients whose lesion did not involve adjacent tissue. Right hemisphere tissue also showed greater activation following treatment, for some patients, in particular the supramarginal gyrus and superior parietal regions. Finally, we found recruitment of neural tissue outside the "normal" network supporting complex syntactic processing (as evinced by our healthy controls), but nevertheless involved in processing language (e.g., Fridriksson et al., 2006). Our findings, therefore, suggest that both right and left hemisphere tissue, including that not normally involved in syntactic processing has potential to be recruited to support recovery.

Conclusions

Treatment of Underlying Forms (TUF), which targets complex Wh-movement sentences, resulted in improved production and comprehension of these structures and generalization to less complex Wh-movement constructions, as has been seen in previous studies with agrammatic aphasic patients. Functional neuroimaging (fMRI) data obtained from healthy speakers performing an auditory verification task reveal activation in the classic left-lateralized language network showing increased activation levels for the contrast of Wh-movement construction processing (object-clefts) versus processing of sentences without Wh-movement (subject clefts). Parts of this network were lesioned in the agrammatic participants, who also underwent pre-treatment and post-treatment neuroimaging, performing the same task. Taking into account the patients' local hemodynamic responses to neural activation, which were correlated with local perfusion levels, the agrammatic participants' pre-post neuroimaging data showed a general shift in activation to more posterior perisylvian and superior parietal cortices, bilaterally, outside of the network primarily activated by healthy controls. This indicates the potential for tissue in these regions to be recruited for syntactic processing. These neuroplasticity data suggest that TUF stimulates the recruitment of alternative cortical areas for processing complex syntactic material.

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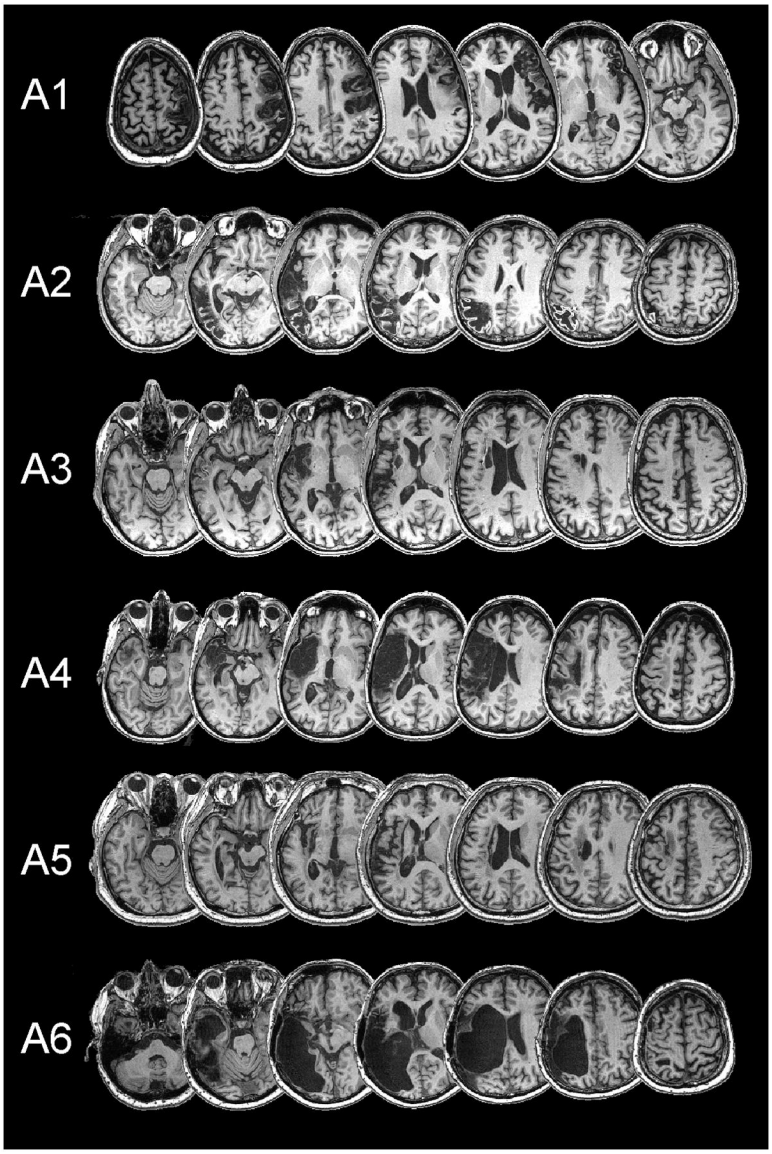

Figure 1.
Aphasic participants' lesions. T1 images.

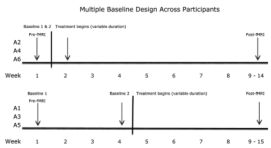

Figure 2.
Experimental Design used in the study.

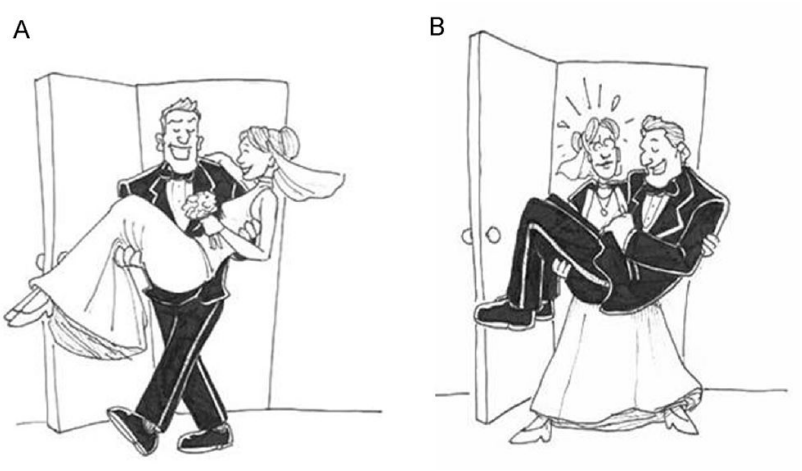

Figure 3.
Example pictures used in the auditory verification task, of reversible actions. Presented with picture 1A or 1B, participants indicate by button press whether the picture matched an auditorily presented sentence, such as *It was the groom that the bride carried*.

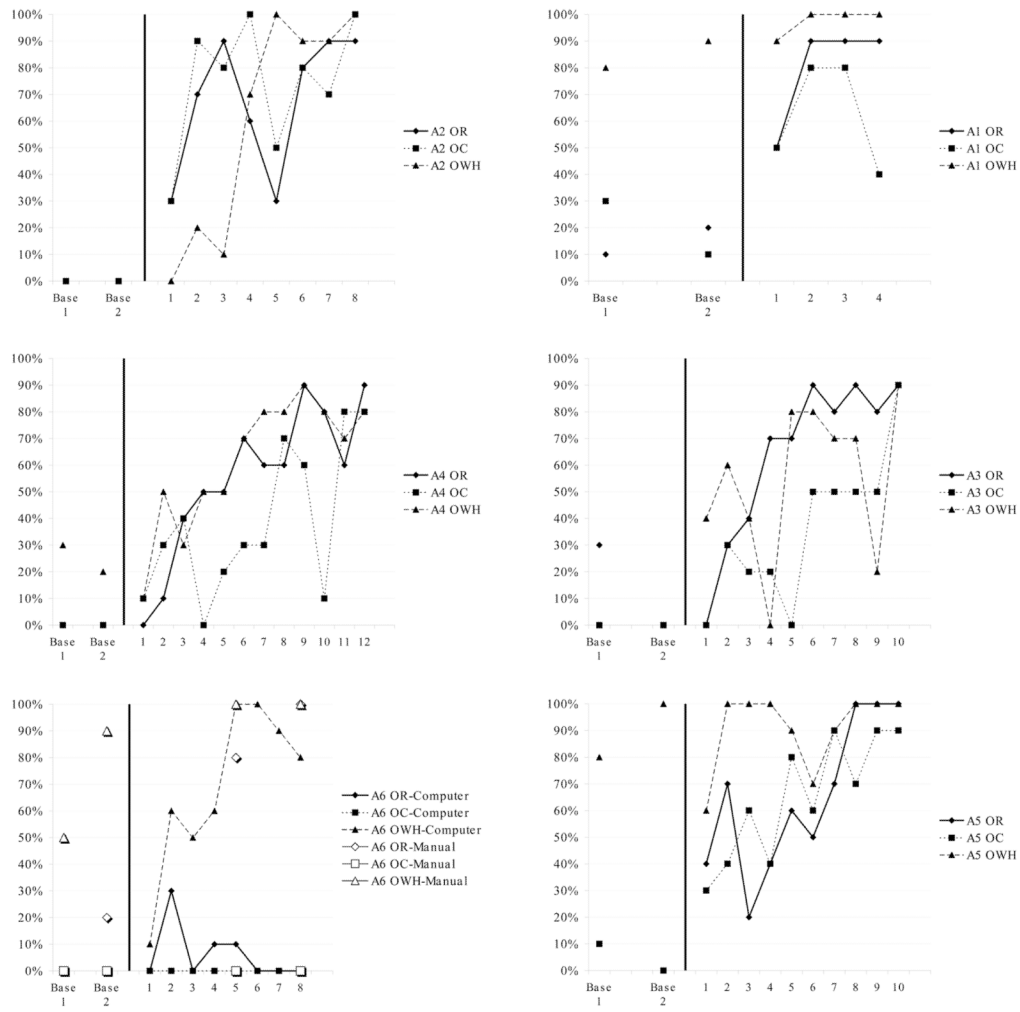

Figure 4.

Percent correct production of object relative (OR), object cleft (OC), and object wh-questions (OWH) structures derived from baseline (Base) and treatment probes (numbered) for individual aphasic participants (A1 – A6). Baseline testing was extended over a four week period for patients A1, A3, and A5, but occurred within 1 week for patients A2, A4, and A6.

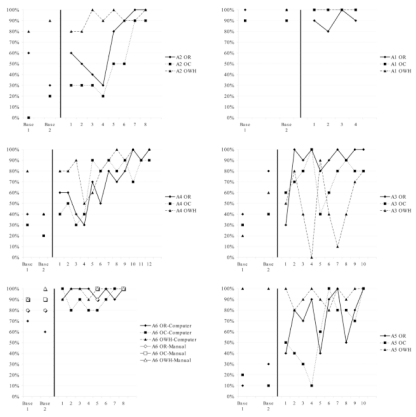

Figure 5.

Percent correct comprehension of object relative (OR), object cleft (OC), and object wh-questions (OWH) structures derived from baseline (Base) and treatment probes (numbered) for individual aphasic participants (A1 – A6). Baseline testing was extended over a four week period for patients A1, A3, and A5, but occurred within 1 week for patients A2, A4, and A6.

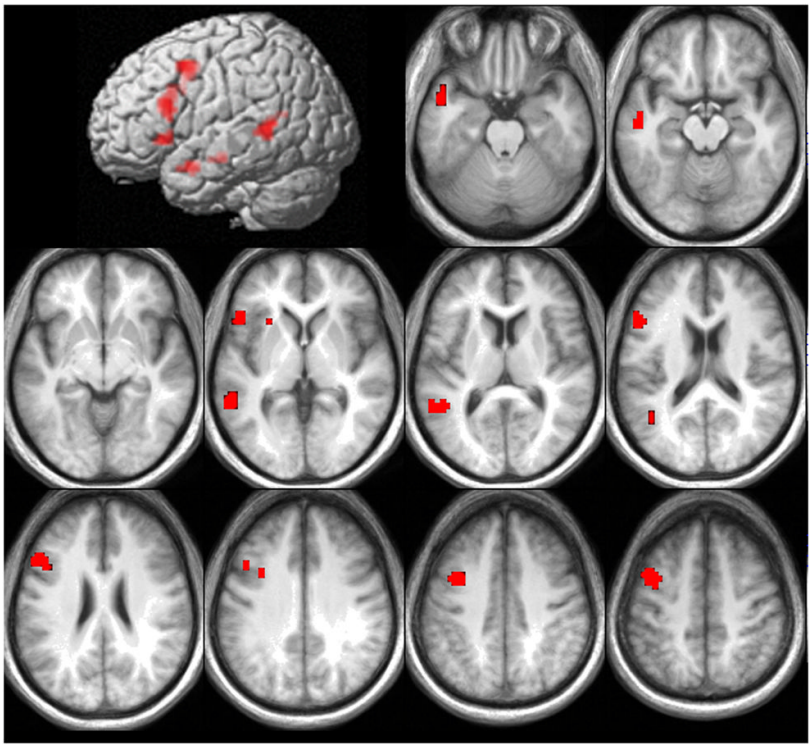

Figure 6.
Significant activations for the contrast OC>SC for healthy volunteer control participants (FDR corrected $p<.05$, $k>3$).

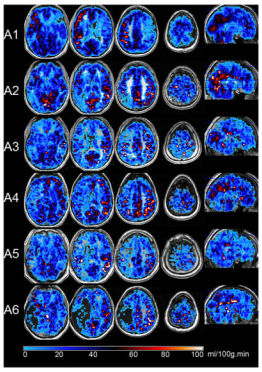

Figure 7.
ASL perfusion imaging results, projected onto four axial slices of each aphasic participant. Participant-specific slice locations are projected onto saggital slices in the right column.

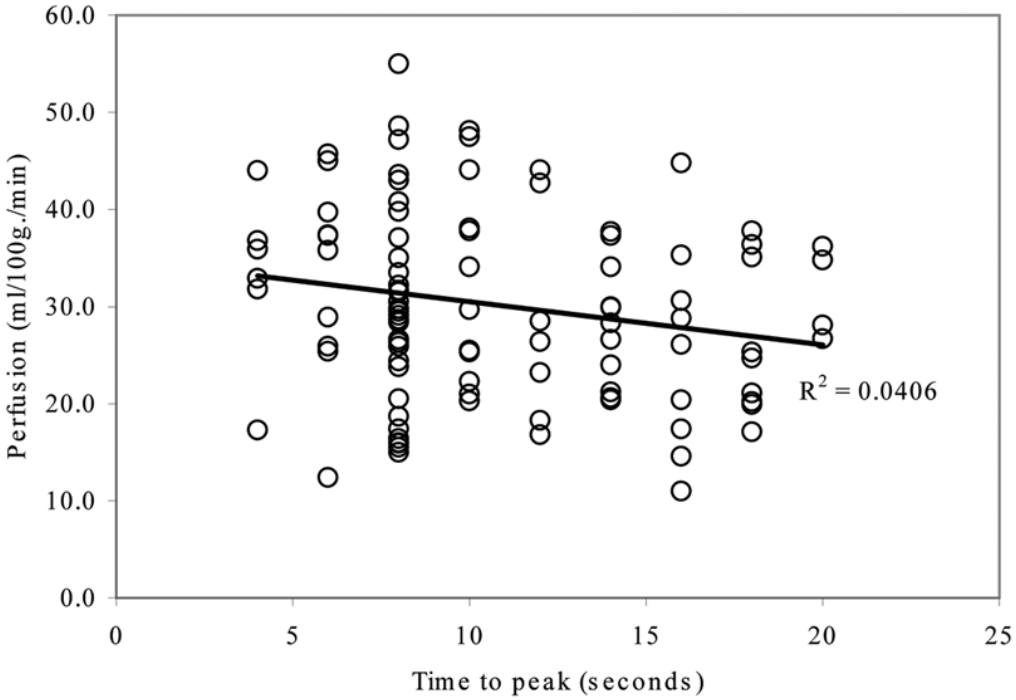

Figure 8.
Scatterplot of aphasic participants' region-specific perfusion values and hemodynamic response time-to-peak, showing a significant negative correlation.

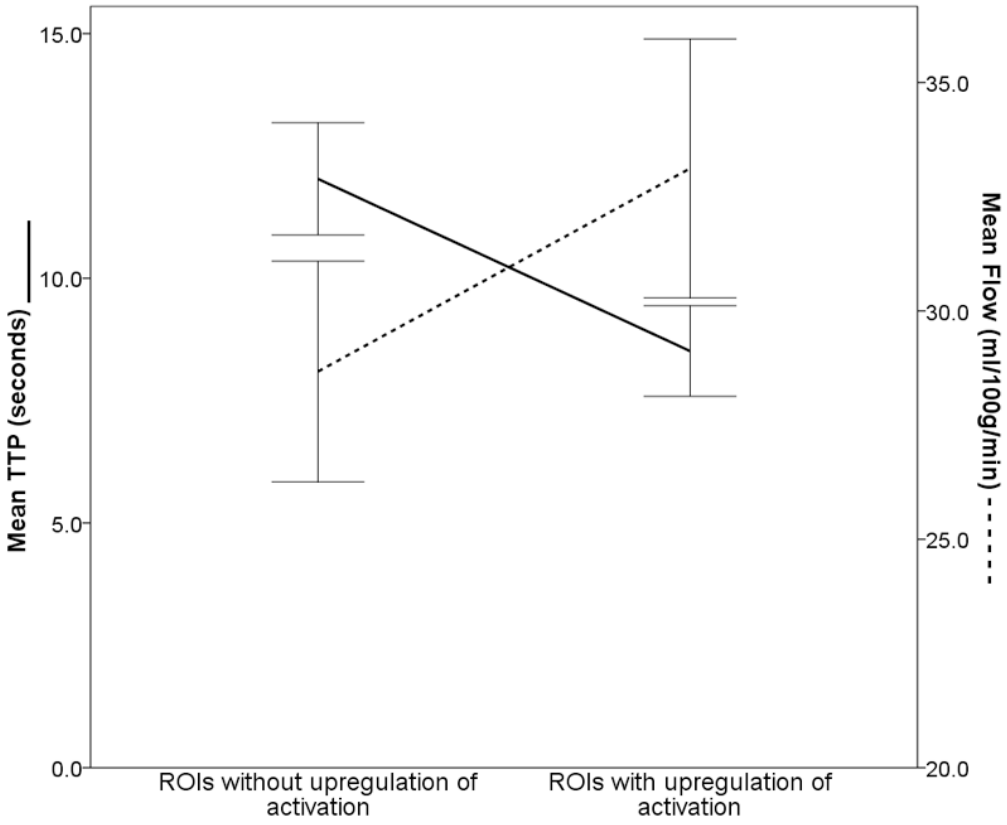

Figure 9.
Mean hrf time-to-peak (TTP) and perfusion levels in ROIs in which upregulation of main-effects activation was seen post-treatment compared to ROIs that did not show upregulation.

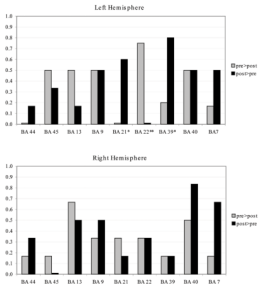

Figure 10.

Proportion of participants with spared tissue in each ROI showing up- and downregulation of main-effects activation levels, by ROI. *Note:* *One participant had no functional tissue in this region, thus proportion based on $n = 5$ participants. ** Two participants had no functional tissue in this region, thus proportion based on $n = 4$ participants.

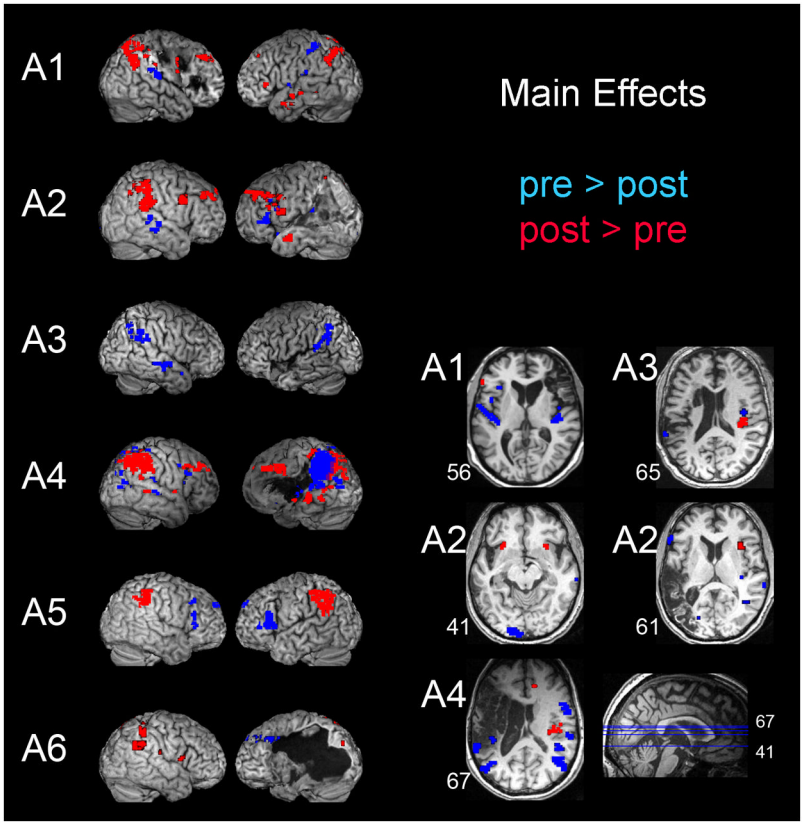

Figure 11.
Main effects for the contrasts pre>post (shown in blue) and post>pre (shown in red) for each aphasic participant (A1 – A6) in the 9 bilateral ROIs, projected onto skull-stripped renderings of their normalized brain images (FDR corrected $p<.05$; $k>3$). Axial slices are shown bottom right for participants with pre-post activation in the insula.

Table 1

Lesion characteristics of the agrammatic participants.

Participants	Etiology	Lesion (structures involved)
A1	CVA (right hemisphere)	Insula, inferior frontal orbital gyrus, inferior frontal pars triangularis, middle frontal gyrus, precentral gyrus, postcentral gyrus, inferior parietal lobule
A2	CVA (left hemisphere)	Inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, inferior parietal lobule, superior parietal lobule, middle occipital gyrus
A3	CVA (left hemisphere)	Insula, inferior frontal orbital gyrus, inferior frontal pars triangularis, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus; putamen; caudate nucleus
A4	CVA (left hemisphere)	Insula, inferior frontal orbital gyrus, inferior frontal pars triangularis, inferior frontal pars opercularis, precentral gyrus, postcentral gyrus, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus; Heschl's gyrus, temporal pole, inferior parietal lobule, parahippocampal gyrus, hippocampus, putamen, caudate nucleus, thalamus
A5	CVA (left hemisphere)	Insula, inferior frontal orbital gyrus, inferior frontal pars triangularis, middle frontal gyrus, superior frontal gyrus, superior temporal gyrus, hippocampus, putamen, caudate nucleus, thalamus
A6	CVA (left hemisphere)	Insula, inferior frontal pars triangularis, inferior frontal pars opercularis, middle frontal gyrus, precentral gyrus, postcentral gyrus, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, temporal pole, inferior parietal lobule, inferior occipital gyrus, fusiform gyrus, hippocampus, putamen, amygdala, caudate nucleus, thalamus

Note. CVA = cerebral vascular accident.

Table 2

Aphasic participants' (A1 – A5) demographic data.

	A1	A2	A3	A4	A5	A6
Age	51	51	59	66	38	66
Gender	M	M	M	F	M	M
Months post-stroke	6	8	24	33	51	146
Handedness	R	R	R	R	R	R
Education (yrs.)	20	12	18	19	19	18
Pre-stroke occupation	University professor	Bartender	Investment banker	Attorney	Medical student	Accountant

Table 3

Language testing data (entry scores) for the agrammatic participants

	A1	A2	A3	A4	A5	A6	Mean
Western Aphasia Battery (WAB)							
Fluency	5	4	4	4	4	4	4.3
Information content	8	8	7	7	9	9	8
Comprehension	9	7.2	9.3	8.7	9.3	9.5	8.8
Repetition	9.2	5.6	7	7.6	8.6	7.8	7.6
Naming	9.6	7.6	7.9	7.3	9.6	9	8.5
Aphasia Quotient	83.6	66.8	72.4	71.2	85	78.5	76.3
Northwestern Assessment of Verbs and Sentences (NAVS)							
Verb Comprehension Test (VCT)	100	100	97	97	100	100	99
Verb Naming Test (VNT)	97	78	67	38	88	88	76
Argument Structure Production Test (ASPT)	98	88	90	88	90	82	89.3
Sentence Production Priming Test (SPPT)							
Active	100	80	80	40	80	100	80
Subject wh-question	100	20	80	40	80	60	63
Subject relative	100	20	40	20	60	40	47
Passive	0	0	60	40	20	0	20
Object wh-question	80	60	0	60	60	0	43
Object relative	0	0	0	0	0	0	0
Total production (mean)	63.3	30	43.3	33.3	50	33.3	42.2
Sentence Comprehension Test (SCT)							
Active	80	100	100	80	100	100	93
Subject wh-question	100	80	100	60	100	100	90
Subject relative	100	100	100	60	100	100	93
Passive	100	20	60	40	60	60	57
Object wh-question	100	80	80	40	100	100	83
Object relative	60	0	60	40	0	60	37
Total comprehension (mean)	90	63.3	83.3	53.3	76.6	86.6	75.5
Narrative language analyses							
MLU	4.78	7.61	7.47	6.52	6.33	5.37	6.35

	A1	A2	A3	A4	A5	A6	Mean
Percent grammatical sentences	28.57	68.18	30.77	38.89	73.39	31.25	45.18
Open:close class ratio	3.05	1.89	1.01	1.02	1.81	1.88	1.78
Noun:verb ratio	2.31	1.75	1.50	1.14	1.33	1.88	1.65
Percent verbs with correct arguments	75.00	62.86	74.44	74.07	33.33	77.78	66.25

Table 4

Effect sizes calculated using production probe data. The bottom two rows show calculations based on computerized (Cohon's *d*) and manual (Chi^2) probe data for subject A6, respectively.

Aphasic Participant	Sentence Type		
	Object Relative	Object cleft	Object wh-questions
A1	3.04[a]	1.50	2.31
A2	4.62[b]	4.33[b]	6.13*[c]
A3	4.33[b]	3.82*[a]	1.80
A4	4.91*[b]	13.28[c]	5.50[b]
A5	4.00[b]	5.02[b]	1.00
A6 computerized	0	0	14.15[c]
A6 manual (Chi^2)	p<.001	NA	p=.37

Note: Effect sizes -

[a] small;

[b] medium;

[c] large (after Robey et al., 1999).

* For these cells, baseline variance was 0, so the SD of the two other sentence types (pooled) was used in the *d* calculation.

Table 5

Pre- to Post-treatment performance on NAVS Sentence Production Priming Test (SPPT) and Sentence Comprehension Test (SCT).

	A1		A2		A3		A4		A5		A6		Mean Scores	
NAVS Subtest	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
SPPT	63.3	77.1	30	42.8	43.3	80	33.3	48.6	50	59.8	33.3	53.6	42.2	60.3
SCT	90	97.1	63.3	62.8	83.3	89	53.3	61.4	76.6	85.7	86.6	85.7	75.5	80.2

Note: NAVS = Northwestern Assessment of Verbs and Sentences.

Table 6

Control group contrast results, as revealed by *t*-tests (FDR corr., $p<.05$, $k>3$).

Contrast	Activation peak	Cluster extent	BA	x	y	z	Cluster size	t-Max
OC > SC	L IFG	MFG	9, 44, 45, 46	−54	18	18	44	4.91
	L IFG		45, 47	−51	21	0	13	4.49
	L insula		13	−30	18	−3	5	4.01
	L MFG	PG	6, 8, 9	−39	6	45	52	5.79
	L STGs	MTG	21, 22	−57	−45	6	42	5.16
	L MTG	STG	21, 38	−48	3	−21	15	5.16
	L MTG, white matter			−51	−18	−12	8	4.18
	L AG		39	−42	−60	15	3	4.18
SC > OC	L insula		13	−42	−3	12	8	5.33

Note: L = left hemisphere; OC = object cleft sentence condition; SC = subject cleft sentence condition; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus; PG = precentral gyrus; AG = angular gyrus.

Table 7

Aphasic participants' scan task performance: mean accuracy and reaction times before and after treatment by sentence type.

		Object Cleft		Subject Cleft		Active		Mean	
		Correct	**RT**	**Correct**	**RT**	**Correct**	**RT**	**Correct**	**RT**
A1	Pre	58.3%	4592	86.7%	3626	91.7%	3789	78.9%	4002
	Post	60.0%	5298	88.3%	4820	95.0%	4336	81.1%	4818[c]
A2	Pre	25.0%	5384	60.0%	4968	51.7%	5460	45.6%	5271
	Post	31.7%	5877	68.3%	5421	56.7%	5828	52.2%	5709[c]
A3	Pre	20.0%	4924	85.0%	4297	86.7%	4423	63.9%	4544
	Post	18.3%	4293	91.7%	3858	83.3%	4201	64.4%	4117[d]
A4	Pre	36.7%	4769	70.0%	5015	58.3%	4675	55.0%	4823
	Post	33.3%	4194	58.3%	4063	61.7%	4355	51.1%	4205[d]
A5	Pre	33.3%	4124	83.3%	3593	88.3%	3741	68.3%	3819
	Post	55.0%[a]	4315	76.7%	3939	68.3%[b]	4188	66.7%	4147[c]
A6	Pre	50.0%	3405	60.0%	3597	56.7%	3767	55.6%	3591
	Post	73.3%[a]	3596	78.3%[a]	3358	78.3%[a]	3733	76.7%	3563

Note:

[a] Significant accuracy improvement ($p<.05$);

[b] Significant accuracy decrease ($p<.05$);

[c] Significant RT increase ($p<.05$);

[d] Significant RT decrease ($p<.05$).

Table 8

Aphasic participants' time-to-peak (TTP) of the hemodynamic response and mean blood flow values by region of interest.

	Participant											
	A1		A2		A3		A4		A5		A6	
Region	TTP	Flow	TTP	Flow	TTP	Flow	TTP	Flow	TTP	Flow	TTP	Flow
L BA 44	10	47.5	10	34.1	12	23.2	8	18.7	8	15.5	14	24.0
L BA 45	8	40.8	14	29.9	12	26.4	8	15.9	16	17.4	8	31.5
L BA 13	8	47.2	8	37.1	8	28.5	10	22.3	8	55.0	12	28.5
L BA 9	6	37.3	8	26.3	18	17.1	8	16.4	16	14.6	10	21.0
L BA 21	4	32.9	8	23.8	18	21.1	6	12.4	16	28.8	.	21.2
L BA 22	4	44.0	.	38.3	18	25.3	8	24.4	16	35.3	.	30.7
L BA 39	10	48.1	16	11.0	4	35.9	6	37.4	8	30.5	.	15.0
L BA 40	4	36.8	10	29.7	20	28.1	8	25.9	16	26.1	12	16.8
L BA 7	4	31.8	14	26.6	4	17.3	8	31.7	8	16.0	16	30.6
R BA 44	12	18.3	10	37.8	20	34.8	8	32.2	14	30.0	14	21.2
R BA 45	10	20.3	10	44.1	20	26.7	20	36.2	14	20.4	8	28.4
R BA 13	8	20.5	8	43.0	8	39.8	6	45.0	6	35.8	6	39.7
R BA 9	10	25.3	8	28.6	18	19.9	8	29.5	16	20.4	6	25.4
R BA 21	10	25.5	8	29.1	8	29.8	8	26.6	14	28.3	14	20.6
R BA 22	18	24.7	12	42.7	18	35.1	10	38.1	14	37.7	14	34.1
R BA 39	6	28.9	16	44.8	18	36.4	8	48.6	8	47.2	8	43.0
R BA 40	8	17.4	12	44.1	18	37.8	6	45.7	14	37.3	8	43.6
R BA 7	6	25.9	8	33.5	18	20.2	6	37.3	8	28.7	8	35.0
mean L	6.4	35.6	11.0	25.4	12.7	22.4	7.8	22.4	12.4	18.9	11.4	24.5
mean R	9.8	22.6	10.2	32.3	16.2	27.9	8.9	33.2	12.0	26.1	9.6	29.7

Note: Empty cells in the TTP columns indicate that no fluctuating hemodynamic response was found in these areas; TTP = in seconds; flow = perfusion, in ml/100g/min. L = left; R = right; BA = Brodmann's areas.

Table 9

Aphasic participants showing significant fMRI activation differences across ROIs (9 left hemisphere; 9 right hemisphere) by contrast, based on true region-specific HRF for each ROI (FDR corrected, $p<.05$, $k>3$).

	ROIs								
	44	**45**	**13**	**9**	**21**	**22**	**39**	**40**	**7**
Pre>Post									
Left Hemisphere		A2	A1	A2		A1	A4	A1	A4
		A4	A2	A5		A3		A3	
		A5	A4	A6		A4		A4	
Right Hemisphere	A4	A5	A1	A4	A2	A2	A4	A1	A4
			A2	A5	A3	A4		A3	
			A3					A4	
			A4						
Post>Pre									
Left Hemisphere	A2	A1	A2	A1	A1		A1	A1	A1
		A2		A2	A2		A4	A4	A2
				A4	A4		A5	A5	A4
							A6		
Right Hemisphere	A2		A2	A1	A2	A4	A4	A1	A1
	A6		A3	A2	A3	A6		A2	A2
			A4	A4				A4	A4
								A5	A6
								A6	