Published in final edited form as:

Neuropsychologia. 2016 April ; 84: 113–126. doi:10.1016/j.neuropsychologia.2015.10.019.

The Relationships between the Amount of Spared Tissue, Percent Signal Change, and Accuracy in Semantic Processing in Aphasia

Jordyn A. Sims¹, Kushal Kapse¹, Peter Glynn², Chaleece Sandberg³, Yorghos Tripodis⁴, and Swathi Kiran¹

1

2

3

4

Abstract

Recovery from aphasia, loss of language following a cerebrovascular incident (stroke), is a complex process involving both left and right hemispheric regions. In our study, we analyzed the relationships between semantic processing behavioral data, lesion size and location, and functional percent signal change from functional magnetic resonance imaging (fMRI) data. This study included 14 persons with aphasia in the chronic stage of recovery (six or more months post stroke) and eight healthy controls who performed semantic processing tasks of determining whether a written semantic feature matched a picture or whether two written words were related or not. Using region of interest (ROI) analysis, we found that percent signal change in left inferior frontal gyrus pars opercularis and pars triangularis, despite significant damage, were the only regions to correlate with behavioral accuracy. Additionally, the more the damage to LIFG, LMTG and AG/SMG, the higher the percent signal change in bilateral superior frontal gyrus, middle frontal gyrus, and anterior cingulate, suggesting that these regions appear to serve as an assistive network in the case of damage to traditional language regions. Relative to controls who showed mainly positive correlations in activation between and within LH and RH ROIs, patients showed positive and negative correlations. Specifically, the right inferior frontal gyrus pars orbitalis is presumed to serve a monitoring function. These results reinforce the importance of the left hemisphere in language processing in aphasia, and provide a framework for the relative importance of left and right language regions in the brain.

Keywords

Aphasia; fMRI; Language recovery; Lesion mapping; Regions of interest (ROI)

1. Introduction

There is already a significant body of research on the neurophysiological mechanisms of recovery within each of the phases of recovery from aphasia. Multiple studies have emphasized the importance of reperfusion of damaged tissue in the acute phase of aphasia recovery (Hillis et al., 2004; Hillis et al., 2002; Reineck, Agarwal, & Hillis, 2005). These studies generally agree that early stages of recovery are likely facilitated by tissue recovery from reperfusion, while later stages of recovery are likely driven by other mechanisms, such as the reorganization structural and functional relationships and learning of compensatory strategies (Hillis & Heidler, 2002).

Saur et al. (2006) studied patients in the sub-acute phase of recovery and suggested that reorganization of activation in patients with left hemisphere strokes follows three phases. In the acute phase patients showed significantly reduced left hemisphere activation. This was followed by a period of increased right hemisphere homologous activation patterns, which correlated with improved language function. In the acute phase, a re-shift of peak activation to the left hemisphere correlated with further improvements in language function. These results indicated that although the right hemisphere may be engaged as a compensatory region, activation of the left hemisphere is more facilitatory for language recovery.

Recent qualitative reviews suggest that there is extensive variability in terms of functional and behavioral characteristics from patient to patient during the chronic phase of recovery. Variables such as lesion location and size influence both activation and task accuracy in the chronic phase. As highlighted above, studies have revealed that while language recovery does occur in both hemispheres, left hemisphere activation is ultimately more effective for long term recovery, and furthermore that the more restored the left hemisphere, the less the recruitment of the right hemisphere (Cao, Vikingstad, George, Johnson, & Welch, 1999; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Jordan & Hillis, 2005; Karbe et al., 1998; Thiel et al., 2013; van Oers et al., 2010; Winhuisen et al., 2007).

More specifically, Fridriksson et al. (2010) found that increased naming accuracy was associated with greater activation in preserved left hemisphere tissue, indicating the importance of the left hemisphere in terms of behavioral accuracy. These results suggest that post-stroke language function is dependent on the activation of preserved tissue in the left hemisphere. Further, Fridriksson, Richardson, Fillmore, & Cai (2012) examined activation of the perilesional cortex which was defined as tissue directly adjacent to the lesion exhibiting hypoperfusion. The boundaries to define perilesional cortex within this specific study were calculated based on group results examining cerebral perfusion (up to 15 mm beyond the lesion). Perilesional activation, particularly in the frontal lobe, is predictive of improved accuracy following anomia treatment. Modulation of posterior areas, primarily in the temporal lobe, predicted decreased semantic paraphasias, while modulation of the parietal lobe predicted decreased phonemic paraphasias. Again, activation of left hemispheric networks appears to be associated with better recovery.

The importance of residual, undamaged activation of left hemisphere language regions is again underscored in a meta-analysis of 12 studies (Turkeltaub, Messing, Norise, &

Hamilton, 2011), in which the authors investigated the influence of lesion location on language recovery. The authors conducted a systematic review in which they compiled study results to achieve an experimental group of 105 patients and a control group of 129 normal control participants, across 16 unique tasks. Patients were divided into two groups: those with lesions in the inferior frontal gyrus (IFG) and those without lesions in the IFG. The study found that normal controls were consistent in their activations during generalized language tasks; normal controls activated left inferior frontal gyrus (LIFG), with particular peaks in left inferior gyrus pars opercularis (LIFGop), left inferior frontal gyrus pars orbitalis (LIFGorb), and left inferior frontal gyrus pars triangularis (LIFGtri), and also activated left middle temporal gyrus (LMTG). Across the 16 unique language tasks, patients with aphasia were consistent in their recruitment mechanisms, depending upon whether the LIFG was damaged or not. Patients with damage to the LIFG showed activation in neighboring ipsilesional regions (left anterior insula, left middle frontal gyrus (LMFG)) as well as right hemisphere homologues (RIFGop, RIFGorb, RIFGtri). Patients without damage to LIFG showed continued activation in in the left hemisphere (LIFG, LMFG, LMTG), and some right hemisphere activation (RMTG and RIFGtri). Taken together, these studies highlight the importance of left hemisphere IFG but do not address when and under what circumstances activation of left hemisphere undamaged regions emerges in patients with aphasia.

The size, or extent, of the lesion also is important in determining the pattern of activation (Allendorfer, Kissela, Holland, & Szaflarski, 2012; Crinion, Holland, Copland, Thompson, & Hillis, 2013). Sebastian and Kiran (2011) found that when examining regions of interest (ROIs) that were active during a picture naming and semantic processing task, larger lesions in the left hemisphere tended to result in greater right hemisphere activation than did smaller lesions in the left hemisphere. This positive relationship between larger lesions and more likely right hemisphere compensation is supported by Grafman (2000), who suggested that adaptation of right-hemisphere homologues is more likely when cortical regions that serve a specific function are entirely destroyed, and that transfer of function is less likely if damage is incomplete.

The relationship between the extent of lesion and language function has also been examined in the literature. One approach, albeit indirect, to understand the effect of lesion on language function is by implementing the Voxel-Based Lesion-Symptom Mapping (VLSM) methodology. VLSM integrates behavioral data and very specific lesion data to identify lesioned regions that most affect specific functions (Bates et al., 2003). Multiple studies have used VLSM to examine data of patients with aphasia (Arévalo, Baldo, & Dronkers, 2012; Baldo, Bunge, Wilson, & Dronkers, 2010; Baldo, Schwartz, Wilkins, & Dronkers, 2006; Baldo, Wilkins, Ogar, Willock, & Dronkers, 2011; Borovsky, Saygin, Bates, & Dronkers, 2007; Kim, Jeon, & Lee, 2010; Magnusdottir et al., 2013; Piras & Marangolo, 2007, 2010). Pertinent to the present study, Dronkers et al. (2004) utilized VLSM in a study of language comprehension, and found that left hemisphere regions including MTG, superior temporal gyrus (STG), the superior temporal sulcus (STS) and angular gyrus (AG), and IFG were involved in language comprehension; specifically, patients with aphasia whose lesions did not affect these areas performed comparable to normal controls in measures of language comprehension. In another study, Walker, et al. (2011) found that

damage to Wernicke's area was not correlated with semantic error production and instead the strongest correlations between semantic errors and lesioned tissue were found in the left anterior temporal lobe. Likewise, Antonucci ((Antonucci, Beeson, Labiner, & Rapcsak, 2008) and Lambon Ralph and colleagues (Lambon Ralph, Ehsan, Baker, & Rogers, 2012) have demonstrated impairments in processing of semantic information in patients with damage to left inferior temporal lobe.

VLSM is an efficient method for mapping behavior onto lesions in chronic stroke patients (Geva, Baron, Jones, Price, & Warburton, 2012). However, it does not provide information regarding whether undamaged tissue is actually engaged in the service of a specific language processing function. Specifically, while a lesion in a region is correlated with an impairment in language function, the inverse is not necessarily true; the lack of a lesion in a region does not necessarily mean that this preserved region is accomplishing that language function, and perhaps evolving that region's role in language function. Further, simply because damage to a region is linked to impaired language function, it does not mean that regions remote to the lesion are also not affected (i.e., dynamic diaschisis (Price, Warburton, Moore, Frackowiak, & Friston, 2001). To answer that question, we need to return to fMRI studies that provide structure function mapping and take into account the amount of lesioned tissue in calculating percent BOLD signal change.

Moreover, while fMRI studies on language recovery broadly suggest that left hemisphere language regions are important for language recovery, studies from normal individuals have shown that these same regions are involved in several specific aspects of language processing including semantic processing, the focus of the present study. Therefore, the goal of the present study was to examine how the extent of signal change in preserved left hemisphere (LH) regions and homologous right hemisphere (RH) regions varies as a function of lesion size in the LH. Within this study, we attempt to build upon our pre-existing knowledge of the processes of language recovery following the onset of aphasia by combining structural, functional and behavioral data to examine the relationship between lesion location, lesion size, and percent signal change in left and right hemisphere regions. Studies have not yet examined the relationships between lesion location, size, and percent signal change, in particular with regards to task accuracy, which can provide information regarding the recruitment of specific language regions during successful and unsuccessful language performance.

As noted above, we examined semantic processing in this project, which has been an important focus of neuroimaging research in aphasia. Recent theories of semantic processing have combined behavioral and anatomical data to explain how we create, manipulate, and utilize linguistic/semantic meaning (Binder & Desai, 2011; Jefferies, 2013; Thompson-Schill, Aguirre, D'Esposito, & Farah, 1999). Specifically, Binder and Desai (2011) suggest that certain regions form a semantic network, processing semantic information through the following steps: first, modality specific stimuli are processed and the semantic network is engaged (this process is thought to be driven by higher-level temporal and inferior parietal regions that store increasingly abstract semantic representations); second, appropriate semantic information is retrieved (this process is thought to employ dorsomedial, inferior prefrontal cortices which are accomplished by the posterior cingulate gyrus and adjacent

precuneus); and finally, any appropriate semantic information is stored (this process is thought to employ a connection between the semantic network and the hippocampal memory system) (Binder & Desai, 2011). The model relies on a meta-analysis completed by Binder, Desai, Graves, & Conant (2009), that examined 120 functional neuroimaging studies focusing on semantics. Across these studies, participants performed different semantic tasks which ranged from category decision, to semantic decisions (such as whether a presented stimulus was living or nonliving), to semantic feature verification. Therefore, regardless of the specific stimuli or variations of the task, it appears that the process of retrieving semantic information engages the same network with some level of consistency.

The present study examined signal change elicited by processing of semantic attributes during the presentation of written words across two tasks. Following Binder and Desai's (2011) framework, the semantic processing tasks required access to visual written input, manipulation of abstract semantic representation, and selection of the appropriate response. Given the task requirements, we selected ROIs for our study that have been shown to be involved in semantic processing, as well as adjacent regions to typical lesions in the LH that result in aphasia. See Table 1 for a list of selected ROIs and their presumed functions. Thus, the ROIs included IFG pars orbitalis (IFGorb), pars opercularis (IFGop), and pars triangularis (IFGtri), the middle frontal gyrus (MFG), superior frontal gyrus (SFG), anterior cingulate cortex (ACC), middle temporal gyrus (MTG), angular gyrus (AG), and supramarginal gyrus (SMG). In this study, we combined AG and SMG (AG/SMG) given their close proximity and overlapping presumed functions, although there are other reports of these regions being distinct in their function Caspers et al. (2011). Of note, we did not separate middle temporal gyrus into sub-regions. In the literature, Vigneau, et al. (2006) identify two peaks, middle temporal lateral and middle temporal posterior, while Price (2012) identifies an anterior middle temporal and a posterior middle temporal peak of activation. Given this variability in the research, and due to the fact that the anatomical atlas we utilized in this study does not distinguish between subregions within the MTG, we retained MTG as one region.

The ROIs were utilized to calculate percent signal change in ipsilesional spared tissue and corresponding homologous regions. We chose the methodological approach of examining anatomically constrained ROI-based percent signal change in apriori regions for two reasons. First, relative to the typical, whole-brain GLM analysis that performs the best fit between canonical HRF and acquired data, percent signal change as calculated in Marsbar (Brett et al., 2002) performs time-locked averaging of data into a condition(s) in a given voxel over the total duration of experiment (Poldrack, 2007), thus providing more information about activation in a particular region. Second, we chose anatomically defined ROIs to examine percent signal change (instead of functional ROIs) because functional ROIs can be inherently very variable in the peak activation location, making it challenging to relate percent signal change to damage across patients. We return to this issue in the methods.

As discussed above, prior research has suggested the involvement of contralesional regions following LH damage, and therefore right hemisphere homologues of the LH ROIs were selected as well.

To summarize, we examined signal change in specific regions of interest including typical language regions, neighboring regions, and contralateral homologues, taking lesion size and location as well as task accuracy into account, when participants were performing a semantic processing task. The following were the specific questions in the study:

- (1) What is the relationship between *task accuracy* on a semantic processing task and *percent signal change* in left and right hemispheric language regions? Further, what is the relationship between *standardized test scores* and *percent signal change* in left and right hemispheric language regions? This analysis was intended to demonstrate which regions were related to accurate task performance. We expected to see increased signal change in frontal and temporal regions previously identified as regions of interest on the semantic processing demands, per the Binder, et al. (2009) review. Further, when participants performed the tasks accurately, we expected percent signal change in these regions to be correspondingly higher.
- (2) What is the relationship between the *amount of damaged tissue* and *percent signal change* within left and right hemisphere regions? This analysis intended to show which regions are associated with greater percent signal change in response to lesioned tissue in the left hemisphere. We expected frontal and temporal regions to be damaged, and hence expected a negative relationship between spared tissue in these regions and percent signal change in other regions in the left and right hemisphere, such that the greater the damage in frontal and temporal language regions, the greater the activation in other left and right hemisphere regions.
- (3) What is the relationship of *percent signal change between regions* within the left and right hemisphere for both patients and healthy controls? In this analysis, we intended to investigate which regions show concurrent increased or decreased percent signal change, indicating their function within a network. We hypothesized that for normal controls positive relationships will emerge between our selected left hemisphere ROIs. For patients, specific regions in the frontal, temporal and parietal lobe would be engaged as a network engaged in the service of successful but residual semantic processing.

2. Materials and Methods

2.1 Participants

Participants with aphasia were 14 persons in the chronic recovery stage of aphasia as a result of a left middle cerebral artery stroke. There were 4 females and 10 males, and the participants' ages ranged from 48 to 74 years. Their time post-stroke varied from 6 months to 13 years post-stroke, with an average of 6 years' time post-stroke. All participants' native language was English and all were right-handed.

Each participant with aphasia was administered the *Western Aphasia Battery- Revised*, WAB-R (Kertesz, 1982), which assesses auditory comprehension, naming, fluency, repetition, reading, and writing. From the WAB-R we also calculated participant's Aphasia Quotients (range = 48 to 99.2), providing a severity rating and assisting in classification of participants into a range of syndromes including Wernicke's, Broca's, Transcortical Motor,

Conduction, and Anomic Aphasias. Participants also completed the *Boston Naming Test*, 2nd edition BNT-2 (Kaplan, Goodglass, & Weintraub, 2001) the mean score was 40 (range = 4 to 57). Additionally, they were administered the 3-picture subtest of the *Pyramids and Palm Trees*, PAPT (Howard & Patterson, 1992), a test that examines non-verbal semantic processing. This test generally suggested that participants' semantic systems were fairly intact with a mean score of 49/52 (range = 39 to 51). In order to assess participants' cognition, they were also administered the *Cognitive Linguistic Quick Test*, CLQT (Helm-Estabrooks, 2001), which elicited a composite severity score, as determined by combining measures of aspects of cognition per the test manual; the great majority of participants were within normal limits, though one participant was severely impaired. The criteria for inclusion were left hemisphere strokes and at least some spared tissue in the LIFG. Based on these criteria, two additional participants were not included in this data set as one had a right hemisphere stroke and another participant had no spared tissue in the LIFG. See Table 2 for a summary of participant data.

A group of healthy normal controls (N = 8, females = 5; age range = 44 – 75 years) with no history of brain damage were recruited to obtain normative data on task-specific activation for the two tasks described below. Exclusionary criteria included neurological disorders such as stroke, transient ischemic attacks, Parkinson's disease, Alzheimer's disease, psychological illness, learning disability, seizures and attention deficit disorders.

2.2 Tasks

fMRI data were acquired while participants participated in one of two semantic language tasks in English; normal controls were split evenly between the two tasks. Participants 1, 5, 6, 8, 11, and 14 performed a semantic feature verification task. Sixty-four picture stimuli, evenly distributed across two categories (birds, vegetables) and typicality (typical, atypical), were used. Participants were presented with a picture prime for one second and then the target stimulus (written phrase) for 4 seconds, for a total of 5 seconds, which was based on pilot data indicating that this was an adequate amount of time for patients to respond. For the experimental condition, these written phrases were comprised of semantic features; through button press, participants indicated whether the feature matched the picture. For the control condition, participants looked a scrambled picture that was either black and white or color, with the written phrases "black and white" or "color" below; again using button press, participants indicated whether the color statement was true or false. All stimuli were balanced between button presses requiring the index finger and middle finger, and were randomized, with each stimulus presentation preceded by a fixation of a cross for a two or four second inter-stimulus interval (ISI) that was randomized.

Participants 2, 3, 4, 7, 9, 10, 12, and 13 performed a word relatedness task. Stimuli were 100 written word pairs (experimental condition), split evenly between abstract and concrete words, and 50 written nonword pairs (control condition). Each stimulus had a duration of 5 seconds, which was based on pilot data indicating that this was an adequate amount of time for patients to respond. For the experimental condition, participants indicated whether the word pairs were related or not using a button press. For the control condition, participants indicated whether paired nonwords were the same or not, again by button press. The

nonwords were obtained from the ARC nonword database (Rastle, Harrington, & Coltheart, 2002). Again, all stimuli were balanced between button presses requiring the index finger and middle finger, and were randomized. Each stimulus presentation was preceded by a fixation cross of two, three, or four second duration as a randomized ISI. Stimuli for both tasks were nouns balanced for length, frequency of occurrence (CELEX, (Vanderwouden, 1990)), and familiarity (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm)(Coltheart, 1981).

While these tasks are unique, both these tasks elicit the same semantic processing steps as pointed out by Binder and Desai (2011), Thompson-Schill, et al (1999), and Jefferies (2013). In both tasks, first words are read and comprehended. Second, semantic meaning is extracted. Finally, this semantic meaning is processed and an appropriate decision made. Given the precedent for combining analyses of tasks that demand the same language functions set by recent reviews (Binder & Desai, 2011; Turkeltaub et al., 2011), combining the analysis is valid for testing the hypotheses outlined above. As a further confirmation, we ran follow-up data analyses with a partial correlation accounting for task.

2.3 Neuroimaging Data Collection

Scans for both tasks were performed at the Boston University Center for Biomedical Imaging using a 3 Tesla Philips Acheiva MRI scanner. Structural T1 scans were taken with 140 sagittal slices, 1 mm³ voxels, 240 × 240 matrix, FOV of 240 mm, flip angle of 8, fold-over direction of AP, TR of 8.2 ms, and TE of 3.8 ms. BOLD signal information was obtained using 31 axial slices (3 mm thick, 0.3 interslice gap), 3 mm³ voxels, 80 × 78 matrix, FOV of 240, a flip angle of 90, fold-over direction of AP, TR of 2000 ms and TE of 35 ms.

2.4 Behavioral Data

Behavioral data from the tasks performed within the fMRI scanner were used to calculate accuracy by dividing the number of correct responses by the number of total stimulus presentations. Accuracy was calculated for both control and experimental conditions.

2.5 Lesion masking

Using structural T1 scan, lesion masks were manually drawn as volume-of-interest files (VOIs) slice-by-slice within MRICRON (Rorden, 2012) for each participant. This was done on each slice of the structural MRI for each participant, generating a binary VOI file. Next, a lesion mask was created by deleting regions covered by the VOI lesion file, generating a version of each participant's brain where the lesion tissue was removed, as in Brett, et al. (2002). In this case, the area within the lesion was given a binary intensity of 0. Then, a lesion map was created by preserving regions covered by the VOI lesion file, generating a file containing only the lesioned tissue. In this case the area within the lesion was given a binary intensity of 1 while the rest of the image was given a binary intensity of 0. This lesion map also was used to generate total lesion volume using the descriptive statistics provided by MRICRON when each lesion map was overlaid onto a normalized brain template.

Reliability for lesion mapping was ensured by the authors of this study by performing a Dice analysis as suggested by Rehm, et al. (2004), as a measure of similarity between lesion maps created by two of the authors. A Dice coefficient of 0 indicates no overlap, while a Dice coefficient of 1 indicates complete overlap. A Dice analysis was performed on lesion maps of 5 of the 14 participants as a confirmation for intra-rater reliability. Each of these comparisons revealed Dice indices of greater than 0.8, with an average of 0.88, indicating that the lesion maps hand-drawn by the authors were consistent.

2.6 fMRI preprocessing

SPM8 (Friston, Ashburner, Heather, Holmes, & Poline, 2009) was used to preprocess the images. Slice timing was performed using functional images, which were referenced to the middle slice. Realign, estimate, and re-slice was performed with registration to the mean slice and re-slice interpolation with 4th degree B-Spline. Structural T1 scans were co-registered to the mean functional image. Segmentation was performed based on co-registered structural images into grey matter, white matter and CSF. A masking image (0-damaged area) was provided during segmentation so that the regions containing a value of zero would not contribute when estimating the various segmentation parameters. The images were then normalized for both functional and structural scans. Lesion maps were also normalized separately with the same normalization parameters.

2.6.1 First level analysis—Statistical analysis of functional data was performed by a mass-univariate approach based on General Linear Models (GLM) in SPM8. Task timings (stimulus onsets and durations) were convolved with the canonical hemodynamic response function (HRF) and its temporal derivative. The timings entered as onsets in the GLM were locked to the onset of each trial (prime). A high pass filter of 128 seconds was used. Motion parameters were included in the model as regressors. The data were not smoothed in order to avoid interpolation from nearby regions or CSF which might extend into the boundaries of specific ROIs selected in this study (Meinzer et al., 2013).

2.7 ROI Analysis

Given the variance across lesioned brains, we elected to utilize anatomical ROIs that were based on evidence for ROIs reported for semantic processing.¹ Importantly, anatomically defined ROIs allowed the examination of the relationship between the amount of signal change within a specific region and the amount of damage within that and other regions across patients.

2.7.1 Definition of structural ROIs—Anatomical ROIs were selected using the AAL atlas within Marsbar (Brett et al., 2002), a toolbox for SPM8. ROIs selected included the IFGorb, IFGtri, IFGop, MFG, SFG, MTG, combined angular and supramarginal gyri (AG/SMG), and the ACC. Each ROI was registered to the template brain during the SPM8 unified segmentation procedure, allowing the warping of each subject's map from native to

¹We initially considered utilizing functional ROIs, and tested functional ROI definition with a portion of our data. However, that resulted in great variability in peak activation location across patients, thereby making it difficult to relate percent signal change to structural damage defined in anatomical regions.

MNI space. We manually verified this as well by overlaying the normalized map onto the normalized T1 to ensure that the boundaries were precisely defined. The normalized lesion map was then subtracted from each of these individual ROIs for each participant. This yielded an ROI containing only the spared tissue for each region for each participant.

2.7.2 Analysis of structural ROIs—We then calculated percent of spared tissue within each of these spared tissue ROIs in MRICRON. This was done by adding individual, normalized spared tissue ROIs as an overlay to a normalized template. By generating the descriptive data for the image, we then derived the volume of the voxels in the spared tissue ROIs in cubic centimeters. Based on the volume data taken from typical anatomical ROIs, the percent spared tissue within each ROI was calculated by dividing the volume of the spared tissue ROI by the typical anatomical ROI volume, thus yielding the percentage of spared tissue in each ROI for each participant.

2.7.3 Extraction of percent signal change from ROIs—For each task, semantic feature t-statistic maps was calculated in a first level GLM analysis (2.6.1). Utilizing the ROI toolbox within Marsbar, the percent BOLD signal change for a specified ROI was calculated for the semantic versus control condition. The event duration for each condition was taken into account in this calculation. This process was repeated for each ROI, for both patients and controls.

2.8 Statistical Analysis

First, a Principal Component Analysis (PCA) was performed as a preliminary tool to explore the structure in the correlation among the percent spared tissue outcomes. This structure was then used to build multivariate models to allow for outcome-specific fixed effects and participant-specific and structure-specific random effects. Then, multivariate mixed-effects linear regression analyses were used to test for the association between significant percent spared to percent signal changes.

Additionally, to examine the extent to which total lesion volume predicted BOLD signal change in the right hemisphere, linear regressions were performed. Partial Pearson correlations accounting for task type examined the relationships between task accuracy and percent spared tissue/signal change, demographic and testing information and percent spared tissue/signal change, and the relationships between signal change across regions for both normal controls and patients.

3. Results

3.1 Lesion Overlap

Across patient participants, the most damage occurred in LIFGop, which was damaged in 13 of 14 participants, with an average of 45% spared tissue. Anteriorly, LIFGtri also showed extensive damage in 13 of 14 participants with an average of 66% spared tissue. Posteriorly, all participants showed damage in LMTG (average 57% spared) and LAG/SMG (average 53% spared). LMFG (average 82% spared) and LIFGorb (average 80% spared) were relatively spared. LSFG (95% spared) and LACC (average of 97% spared) were not lesioned

in most participants. See Table 3 and Figure 1 for a summary of damage within regions for each participant.

3.2 Task Accuracy and Signal Change

Based on a paired t-test across participants, control condition accuracy (mean 88% accuracy, SD of 26%) was significantly higher than experimental, semantic processing task accuracy (mean 75% accuracy, SD of 18%, Task 1 average accuracy 76%, Task 2 average accuracy 74%), ($t(13) = -3.62, p < 0.003$), indicating that for patients, semantic processing was more demanding than the control conditions. Task accuracy significantly correlated with signal change in LIFGop ($r = 0.54, p = 0.05$) and LIFGtri ($r = 0.54, p = 0.05$), suggesting that LIFGop and LIFGtri were associated with higher accuracy on the semantic processing task. Additionally, correlations between task accuracy and lesion extents were performed, however they did not yield significant correlations.

3.3 Demographic and Testing Correlations

To examine the relationship between language impairment (as measured by the *WAB-R*, *BNT-2*, and *PAPT*), spared tissue, and percent signal change, we examined Pearson correlations between test scores on the *WAB-R*, *BNT-2*, and *PAPT* and the amount of spared tissue, BOLD signal change, and experimental task accuracy. We used the Aphasia Quotient (*AQ*) from the *WAB-R*, a score reflecting overall language severity of aphasia across language tasks. This revealed significant positive correlations between the *WAB-R AQ* and amount of spared tissue in the LMTG ($r = 0.714, p = 0.05$), and in the LAG/SMG ($r = 0.60, p = 0.05$), indicating that less severe language impairment (the higher the *AQ*) was associated with greater sparing of tissue in LMTG, and LAG/SMG.

Using the total number of correctly named pictures from the *BNT-2*, the amount of spared tissue in LMTG ($r = 0.61, p = 0.05$) and in LAG/SMG ($r = 0.58, p = 0.05$), suggesting that the greater amount of spared tissue in these regions, the more pictures were named correctly.

For the *PAPT*, a non-verbal semantic processing task, accuracy correlated positively with the amount of spared tissue in the LMFG ($r = 0.52, p = 0.06$) suggesting that the more spared tissue in this region, the better semantic processing. Additionally, *PAPT* score correlated positively with experimental accuracy on our semantic processing tasks ($r = 0.84, p = 0.05$).

We calculated correlations between percent BOLD signal change and standardized test scores; however, these did not yield significant results. We chose not to examine the correlations between age and time post-stroke, as our data were more weighted towards older adults who were several months post their stroke onset.

3.4 Percent Spared Tissue and Percent Signal Change

3.4.1 Principal Component Analysis (PCA) results—A PCA was used as an exploratory analysis to examine the relationship between percent spared tissue and percent signal change and influence further analyses based on groupings seen within the PCA. A scree plot was used to determine the possible number of factors underlying these components as well as the Kaiser criterion of eigenvalues greater than 1.00. Based on a

varimax normalized matrix, 13 factors were considered factors of interest, the first four of which explained 79.6% of the variance in the data (See Table 4). Structures with scores greater than 0.5 were assigned to each factor and there were both positive and negative factors in each principal component. The positive values within factor 1 consisted of the amount of spared tissue in LIFGorb, LMTG, and LAG/SMG. Negative components of factor 1 included amount of spared tissue in LSFG, LACC and the amount of percent signal change in LIFGop, LMFG, LSFG, RIFGop, RIFGtri, RMFG, RSFG, RMTG, RAG/SMG, and RACC. It should be pointed out that all of the RH contralesional regions' signal change emerged in this factor, except for RIFGorb. Within factor 2, positive values included spared tissue in LIFGop, LIFGtri and LMFG and percent signal change in LACC, RIFGorb. The only negative value in this factor was percent signal change in LIFGtri. Factor 3 included positive components of percent signal change in LAG/SMG. Finally, factor 4 included positive components included signal change from LIFGorb and LMTG and experimental task accuracy.

3.4.2 Multivariate models results—We structured our multivariate models based on the results of our PCA analysis. Outcomes of percent spared for each participant were correlated using a single between-outcome correlation by applying a compound-symmetry model for the covariance matrix. Hence, two levels of correlations were modeled in the outcomes: i) correlations of all percent spared tissue from the same patients and ii) correlations of all percent signal change from the same structure (e.g., LIFGop % signal, LIFGtri % signal, LMTG % signal, LACC % signal, and RIFGorb % signal are assigned to the same factor as indicated by the PCA). These multivariate analyses are more realistic models of the outcomes than using independent regression models for each outcome. Since all information within each participant was utilized, we are able to provide more interpretable and consistent results than simpler statistical models. Moreover, the problem of multiple comparisons is removed when using these models (Gelman, Hill, & Yajima, 2012). These multivariate models provide higher power for detecting small but clinically important differences compared to independent regression models for each outcome (Goldstein, 2010).

Table 5 indicates t-values for the positive and negative correlations. T-values greater than 2.28 are significant after correction for multiple comparisons (Benjamini & Hochberg, 1995). Both negative and positive correlations were found (see Figure 2). Positive correlations imply that the greater the amount of spared tissue, the higher the BOLD signal change (or the lower the amount of damaged tissue, the lower the BOLD signal change). Positive correlations were observed between the amount of spared tissue in LSFG and LACC with percent signal change in all ROIs that were examined.

Meanwhile, negative correlations imply that the lower the amount of spared tissue, the higher the BOLD signal change (or the higher the amount of spared tissue, the lower the BOLD signal change). Negative correlations were observed between (a) the amount of spared tissue in LIFGop and percent signal change in LACC, (b) the amount of spared tissue in LIFGtri and percent signal change in LAG/SMG, LMFG, LSFG, RSFG, LACC, and RACC; (c) the amount of spared tissue in LIFGorb and percent signal change in RIFGorb, LMTG, LMFG, RMFG, LAG/SMG, LSFG, RSFG, LACC, and RACC; (d) the amount of spared tissue in LMTG and percent signal change in LAG/SMG, LMFG, LSFG, RSFG,

LACC, and RACC; and (c) the amount of spared tissue in LAG/SMG and percent signal change in bilateral anterior regions including LMFG, RMFG, LAG/SMG, LSFG, RSFG, LACC, and RACC.

3.4.3 Lesion volume and right hemisphere BOLD signal results—To examine the extent to which right hemisphere BOLD signal change was driven by the total lesion volume in the LH, 8 linear regressions were completed. None of the regressions were significant and are hence not discussed further.

3.5 Percent Signal Change among Regions

To understand how percent signal change was affected across regions, a Pearson partial correlation matrix controlling for task was calculated using the percent signal change data for both patients and normal controls.

3.5.1 Pearson partial correlation matrix results for controls—For controls, after accounting for task as a covariate, almost all correlations between regions were positive (see Table 6A, Figure 3). Specifically, LIFGop, LIFGorb, and LIFGtri were found to be correlated positively with one another, suggesting that they work as a unit. Additionally, all LIFG regions were found to correlate positively with LAG/SMG, suggesting anterior to posterior connections. Other LH regions were also correlated with each other including LSFG and LAG/SMG, LMFG and LIFG, and LACC and LIFG/LMFG. Interestingly, several cross-hemispheric correlations were also significant: RSFG and LMTG, RIFGorb and LAG/SMG, RMTG and LAG/SMG, LIFGtri and RIFGop, and LMTG and RMTG.

3.5.2 Pearson partial correlation matrix results for patients—The most striking differences in the correlation matrices between the controls and the patients is that while correlations for controls were mostly all positive, several positive and negative correlations emerged for the patients (see Table 6B, Figure 3). Like the controls, LIFGop, LIFGorb, and LIFGtri were found to be correlated positively with one another for the patient group, (except LIFGop and LIFGorb). Additionally, LIFGtri and LIFGop were found to correlate positively with LMFG, suggesting strong frontal connections.

The correlation matrix also revealed many positive correlations within right hemisphere regions, including RIFGop, RIFGtri, RMFG, RMTG, and LAG/SMG. Additionally, percent signal change in both RSFG and RMFG correlated positively with 6 of 8 other RH regions and RIFGop correlated positively with 5 of the 8 other RH regions. Of interest, RIFGorb stood out as the only region to demonstrate significant negative correlations, correlating negatively with LIFGop and LIFGtri. Several regions also demonstrated positive cross-hemisphere correlations including LIFGop and RIFGop, LMFG and RMFG, LSFG and RMFG, and LACC and RACC.

4. Discussion

The overall goal of our study was to examine the contribution of spared tissue in the recovered language network in patients with aphasia. Specifically, we sought to (1) assess the relationship between task accuracy and percent signal change in left and right language

ROIs, and to examine the relationship between test scores, percent spared tissue and percent signal change testing the hypothesis that increased signal change in LH frontal and temporal regions would be correlated with increased task accuracy; (2) analyze the relationship between the amount of damaged tissue and percent signal change in ROIs, testing the hypothesis that greater damage in frontal and temporal regions would be negatively correlated with signal change in those areas, and that greater damage to these regions would be correlated with percent signal change in RH homologues as well as undamaged LH ROIs; and finally, (3) evaluate the relationship between percent signal change across regions, for both patients and controls anticipating that we would find positive correlations between the percent signal change in frontal, temporal, and parietal regions in the left and right hemispheres for both groups.

Before we examine our results and their interpretation in greater detail, let us first examine percent signal change relationships between ROIs for the healthy controls. The Pearson partial correlation matrix for controls revealed that subregions (triangularis, opercularis and orbitalis) within LIFG were highly correlated with each other and functioned as a unit. Predominantly positive correlations were observed between LH ROIs within the same hemisphere (LIFG, LAG, LMFG, and LSFG), RH ROIs within the same hemisphere (RIFG, RMTG, RAG, RSFG) and cross-hemispheric ROIs (LIFG-RIFG; LMTG-RMTG; LMTG-RSFG; LAG/SMG-RIFG, LAG/SMG- RIFG). These controls represent the normal “optimal” relationship between ROIs within- and across-hemisphere in the absence of any damage to the left hemisphere. In contrast, when we examine the effects of lesion on this language network, several interesting findings emerge.

In persons with aphasia, we found that while the LIFG, LMTG and LAG/SMG were the most damaged ROIs in our population, these were also important regions associated with successful semantic processing during the fMRI task as well as on standardized language assessments. First, task accuracy was significantly correlated with percent signal change in LIFGop and LIFGtri. Second, the less spared LIFG, LMTG and LAG/SMG regions were the higher the percent signal change in LACC and LSFG. And, the more spared LSFG and LACC regions were, the more the percent signal change in all LH ROIs and RH ROIs.

Third, the negative correlations between percent spared tissue and percent signal change are very informative as they indicate which ROIs exhibit high percent signal change relative to lesions to specific LH ROIs. As noted above, the amount of spared tissue in LIFG, LMTG and LAG/SMG correlated with percentage signal change in bilateral ACC and SFG. Notably, however, the amount of spared tissue in LIFG, LMTG and LAG/SMG was also negatively correlated with the percent signal change in LMFG and to a lesser extent RMFG (see Figure 2).

Fourth, even though our methods segregated the subregions of the inferior frontal gyrus into triangularis, orbitalis and opercularis, these regions emerged as a cluster of correlated signal change in both patients and controls. Other ROIs that exhibited correlated percent signal change included RH ROIs comprising IFG, MTG and AG/SMG (see Figure 3) and cross-hemispheric homologues (LIFGop - RIFGop, LMFG - RMFG, LSFG - RMFG, and LACC - RACC) (see Table 6). Interestingly, RIFGorb appears to be isolated from the rest of the right

hemisphere, and only correlated positively with LACC and correlated negatively with LIFGop and LIFGtri.

We will discuss each of these results in further detail in the context of our research questions.

4.1 Task Accuracy and Percent Signal Change

In terms of accuracy correlations, we found that task accuracy was correlated with signal in LIFGop and LIFGtri, suggesting that the more accurate participants were on a task, the stronger the signal in LIFGop and LIFGtri. This is intuitive, as these regions are typically responsible for semantic processing (Ruff, Blumstein, Myers, & Hutchison, 2008) and, thus, should be more effective at completing a semantic processing task (see Table 1).

4.2 Language Impairment and Spared Tissue

We found several notable relationships between language impairment and the amount of spared tissue, BOLD signal change, and experimental task accuracy. First, severity of aphasia (as measured by AQ from WAB-R) and the better picture naming (as measured by the BNT-2) were correlated with the amount of spared tissue in LMTG, and LAG/SMG, such that less severe aphasia was linked with more sparing of tissue in these traditional language regions. These results are consistent with recent VLSM studies highlighting the role of traditional language regions in language impairment (Dronkers et al., 2004) and reinforce the importance of these regions for processing language in general and for picture naming in particular.

Furthermore, we found that the amount of spared tissue within LMFG regions was related to non-verbal semantic processing (as measured by the PAPT). These findings are consistent with studies that have indicated that MFG is involved in semantic processing (Binder et al., 2009). Alternately, Fedorenko et al. (Fedorenko, Duncan, & Kanwisher, 2013) found that in typical brains, a set of regions in the frontal and parietal lobes, including MFG, are activated across domains and tasks, from arithmetic, to working memory. Additionally, the more challenging a task, regardless of domain, the greater the demand on these regions (Fedorenko et al., 2013). This is further supported by a recent meta-analysis study from Geranmayeh, et al. (Geranmayeh, Brownsett, & Wise, 2014), which suggests that there are domain-general systems that enable cognitive control and attention. It is feasible that provided our participants' level of aphasia, our semantic processing task might be challenging, resulting in greater engagement of these frontal and parietal regions. Importantly, the finding that the less spared the tissue in LIFG, LMTG, and LAG/SMG was associated with increased signal change in LMFG lends further credence to the speculation that even with some degree of damage, LMFG was an important region engaged in semantic processing. Moreover, these domain-general systems would likely be highly necessary given the level of difficulty of our task for patients with aphasia.

4.3 Spared Tissue and Signal Change

Based on the PCA and our combined findings from the multivariate analysis, two major findings emerge. First, it appears that when the anterior regions of LSFG and LACC are

more spared, more bilateral anterior signal change is observed. Additionally, LSFG and LACC emerge as regions whose activation is correlated positively with signal change in all ROIs that were examined. This suggests that LSFG and LACC may perform some sort of coordinating or regulatory role within the language network, consistent with other work in our laboratory (Kiran, Meier, Kapse, & Glynn, 2015; Sandberg, Bohland, & Kiran, 2015).

Second, it appears that the more damage there is in traditional language regions including LIFG, LMTG and LAG/SMG, the more activation there is in anterior bilateral SFG, ACC regions and LMFG. Taken together with the findings of correlation between task accuracy and signal change in LIFG and performance on standardized tests a spared tissue in LMTG and AG/SMG, although these regions are damaged they are engaged in semantic processing. Moreover, the more the damage to these regions the more the supportive regions such as SFG and ACC are engaged.

4.4 Signal Change Relationships across Regions

The signal change relationships across regions and groups provided several important observations. While the normal controls showed mostly positive correlations between ROIs, patients showed both positive and negative correlations. For both groups, LIFG semantic processing regions (LIFGop, LIFGorb, and LIFGtri) were correlated positively with one another. Additionally, RH homologues (RIFGop, RIFGtri, RMFG, RMTG, and RAG/SMG) correlated positively with one another for the patients, but for controls these regions were correlated with left hemisphere regions. Finally, cross hemispheric correlations were observed more for controls whereas right hemisphere correlations were more for patients.

The only region that displayed negative correlations was RIFGorb with regions such as LIFGtri and LIFGop and positively correlated with LACC. Given the ACC's role in monitoring language processing, it is possible that RIFGorb works with LACC in this function. This will be discussed in greater detail below.

Notably in the percent signal change correlation analysis, for both patients and controls, LMFG was an important hub of correlated signal change across LH and RH ROIs. However, only for the patients (but not controls) RMFG was also a hub of several positive correlations, correlating with 8 other ROIs (LIFGop, RIFGop, RIFGtri, LMFG, RSFG, RMTG, RAG/SMG, and RACC). As noted before, LMFG is associated with domain-general cognitive control for both language and non-language tasks, thus termed part of a multiple demands network and is thought to mediate different types of domain-general behavior, including goal maintenance, selection of strategies for task completion, and performance monitoring (Fedorenko et al., 2013). With regards to RMFG, it is worth pointing out that in a separate study examining changes in task-based effective connectivity after rehabilitation in patients with aphasia, the connections between RIFG and MFG were the most modulated across patients (Kiran et al., 2015). These results highlight the potentially regulatory role of the frontal regions during language recovery, and future work needs to explore this possibility in greater detail.

4.5 The Isolation of RIFGorb

In the patient data, the question of RIFGorb's role raises interesting questions. While subregions within the LIFG emerged as one unit based on correlation results; subregions in the RIFG did not display this pattern, due to RIFGorb's seeming isolation. RIFG has been implicated in monitoring and attention (Stuss & Alexander, 2007); however, based on recent research from Aron, *et al.* (2014), it appears that RIFG may not be solely responsible for monitoring and attention, but is also likely involved in inhibitory breaking, both in terms of complete stopping of an action and of pausing an action. It should be noted, however, that the work of Aron, *et al.* (2014) refers to the RIFG in general, while our research implicates RIFGorb only. The involvement of RIFGorb in an inhibitory, breaking function could explain our findings of negative relationships between RIFGorb signal change and signal change in LIFGop and RIFGtri – perhaps RIFGorb is acting as an inhibitor of these regions for these patients.

An alternate, but not opposing view, is that RIFGorb and bilateral , SFG and ACC form a monitoring network that inhibits actions as needed. Signal change in RIFGorb correlates positively with LACC, which in turn correlates positively in terms of signal change with its contralateral homologue, RACC. Additionally, the percent spared tissue in SFG and LACC correlated positively with bilateral signal change in all regions; again suggesting a potential regulatory role. Given the regulatory processes that ACC appears to participate in, studies on RIFGorb's participation in monitoring, and our data as summarized here, it is possible that these regions form a monitoring network. These results are speculative at this point, and future work needs to be done to identify the precise relationships between RIFGorb, ACC, and other language regions in the brain during language processing tasks.

4.6 Limitations of the study

As discussed in the introduction, we intentionally selected a diverse group of patients and healthy controls that had participated in two semantic processing tasks. Additionally, the correlations for the healthy controls are very similar to the patients, with some important differences and lend further support to our conclusions. Nonetheless, we cannot rule out the possibility that even though the tasks engage the same type of semantic processing abilities, they may not evoke the same magnitude of BOLD signal change across the ROIs we examined to the same degree. Additionally, these subtle differences may be even more pronounced with differing lesion sites and behavioral language impairment profiles. Future work needs to examine a larger and more homogenous sample of patients (constrained either by lesion site or behavioral profile) to carefully examine the degree of activation in specific regions. Such work is ongoing in our lab currently.

4.7 Conclusions

Taken as a whole, our results concerning task accuracy, spared tissue, and percent BOLD signal change suggest a nuanced relationship between damaged regions and signal change in other regions. Our findings are in line with previous research that suggests that recovery of function in left language regions and activation of residual left hemisphere tissue is essential for recovery, though some recovery may involve recruitment of areas in the right hemisphere as well. Indeed, these right hemisphere regions show extensive positive signal

change correlations with each other, with the exception of RIFGorb. RIFGorb stands out as isolated amongst right hemisphere regions, appearing to be part of a potentially regulatory network involving bilateral ACC.

Acknowledgments

This research was supported by the National Institute on Deafness and Other Communication Disorders/National Institute of Health grants to Swathi Kiran (grant number 1K18DC011517-01) and to Chaleece Sandberg (grant number 5F31DC011220).

References

- Abutalebi J, Annoni JM, Zimine I, Pegna AJ, Seghier ML, Lee-Jahnke H, Khateb A. Language control and lexical competition in bilinguals: an event-related fMRI study. *Cereb Cortex*. 2008; 18(7): 1496–1505. [PubMed: 17947346]
- Abutalebi J, Rosa PA, Tettamanti M, Green DW, Cappa SF. Bilingual aphasia and language control: a follow-up fMRI and intrinsic connectivity study. *Brain Lang*. 2009; 109(2-3):141–156. doi:S0093-934X(09)00040-6 [pii]. 10.1016/j.bandl.2009.03.003 [PubMed: 19427522]
- Allendorfer JB, Kissela BM, Holland SK, Szaflarski JP. Different patterns of language activation in post-stroke aphasia are detected by overt and covert versions of the verb generation fMRI task. *Med Sci Monit*. 2012; 18(3):CR135–137. [PubMed: 22367124]
- Antonucci SM, Beeson PM, Labiner DM, Rapsak SZ. Lexical retrieval and semantic knowledge in patients with left inferior temporal lobe lesions. *Aphasiology*. 2008; 22(3):281–304.10.1080/02687030701294491 [PubMed: 19756227]
- Arévalo AL, Baldo JV, Dronkers NF. What do brain lesions tell us about theories of embodied semantics and the human mirror neuron system? *Cortex*. 2012; 48(2):242–254.10.1016/j.cortex.2010.06.001 [PubMed: 20621292]
- Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. *Trends Cogn Sci*. 201410.1016/j.tics.2013.12.003
- Axelrod V, Bar M, Rees G, Yovel G. Neural Correlates of Subliminal Language Processing. *Cereb Cortex*. 201410.1093/cercor/bhu022
- Baldo JV, Bunge SA, Wilson SM, Dronkers NF. Is relational reasoning dependent on language? A voxel-based lesion symptom mapping study. *Brain Lang*. 2010; 113(2):59–64.10.1016/j.bandl.2010.01.004 [PubMed: 20206985]
- Baldo JV, Schwartz S, Wilkins D, Dronkers NF. Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *J Int Neuropsychol Soc*. 2006; 12(6): 896–900.10.1017/S1355617706061078 [PubMed: 17064451]
- Baldo JV, Wilkins DP, Ogar J, Willock S, Dronkers NF. Role of the precentral gyrus of the insula in complex articulation. *Cortex*. 2011; 47(7):800–807.10.1016/j.cortex.2010.07.001 [PubMed: 20691968]
- Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, Dronkers NF. Voxel-based lesion-symptom mapping. *Nat Neurosci*. 2003; 6(5):448–450.10.1038/nn1050 [PubMed: 12704393]
- Bedny M, Hulbert JC, Thompson-Schill SL. Understanding words in context: the role of Broca's area in word comprehension. *Brain Res*. 2007; 1146:101–114. doi:S0006-8993(06)02984-2 [pii]. 10.1016/j.brainres.2006.10.012 [PubMed: 17123486]
- Benedek M, Beaty R, Jauk E, Koschutnig K, Fink A, Silvia PJ, Neubauer AC. Creating metaphors: The neural basis of figurative language production. *Neuroimage*. 2014; 90:99–106.10.1016/j.neuroimage.2013.12.046 [PubMed: 24384149]
- Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*. 1995; 57(1):289–300.
- Binder JR, Desai RH. The neurobiology of semantic memory. *Trends Cogn Sci*. 2011; 15(11):527–536.10.1016/j.tics.2011.10.001 [PubMed: 22001867]

- Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex*. 2009; 19(12):2767–2796. doi:bhp055 [pii]. 10.1093/cercor/bhp055 [PubMed: 19329570]
- Bohrn IC, Altmann U, Jacobs AM. Looking at the brains behind figurative language--a quantitative meta-analysis of neuroimaging studies on metaphor, idiom, and irony processing. *Neuropsychologia*. 2012; 50(11):2669–2683.10.1016/j.neuropsychologia.2012.07.021 [PubMed: 22824234]
- Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci*. 2002; 25:151–188. 112701.142946 [pii]. 10.1146/annurev.neuro.25.112701.142946 [PubMed: 12052907]
- Booth JR, Burman DD, Meyer JR, Gitelman DR, Parrish TB, Mesulam MM. Functional anatomy of intra- and cross-modal lexical tasks. *Neuroimage*. 2002; 16(1):7–22.10.1006/nimg.2002.1081 [PubMed: 11969313]
- Borovsky A, Saygin AP, Bates E, Dronkers N. Lesion correlates of conversational speech production deficits. *Neuropsychologia*. 2007; 45(11):2525–2533.10.1016/j.neuropsychologia.2007.03.023 [PubMed: 17499317]
- Brett, M.; Anton, J.; Valabregue, R.; Poline, J. Region of interest analysis using an SPM toolbox. Paper presented at the 8th International Conference on Functional Mapping of the Human Brain; Sendai, Japan. 2002.
- Cao Y, Vikingstad EM, George KP, Johnson AF, Welch KM. Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke*. 1999; 30(11):2331–2340. [PubMed: 10548667]
- Cappa SF. Imaging semantics and syntax. *Neuroimage*. 2012; 61(2):427–431.10.1016/j.neuroimage.2011.10.006 [PubMed: 22019859]
- Caspers S, Eickhoff SB, Rick T, von Kapri A, Kuhlen T, Huang R, Zilles K. Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. *Neuroimage*. 2011; 58(2):362–380.10.1016/j.neuroimage.2011.06.027 [PubMed: 21718787]
- Chertkow H, Bub D, Deaudon C, Whitehead V. On the status of object concepts in aphasia. *Brain Lang*. 1997; 58(2):203–232.10.1006/brln.1997.1771 [PubMed: 9182748]
- Coltheart M. The MRC psycholinguistic database. *Quarterly Journal of Experimental Psychology*. 1981; 33A:497–505.
- Crinion J, Holland AL, Copland DA, Thompson CK, Hillis AE. Neuroimaging in aphasia treatment research: quantifying brain lesions after stroke. *Neuroimage*. 2013; 73:208–214.10.1016/j.neuroimage.2012.07.044 [PubMed: 22846659]
- Dronkers NF, Wilkins DP, Van Valin RD, Redfern BB, Jaeger JJ. Lesion analysis of the brain areas involved in language comprehension. *Cognition*. 2004; 92(1-2):145–177.10.1016/j.cognition.2003.11.002 [PubMed: 15037129]
- Fedorenko E, Duncan J, Kanwisher N. Broad domain generality in focal regions of frontal and parietal cortex. *Proc Natl Acad Sci U S A*. 2013; 110(41):16616–16621.10.1073/pnas.1315235110 [PubMed: 24062451]
- Fiez JA. Phonology, semantics, and the role of the left inferior prefrontal cortex. *Hum Brain Mapp*. 1997; 5(2):79–83. [PubMed: 10096412]
- Fridriksson J, Bonilha L, Baker JM, Moser D, Rorden C. Activity in preserved left hemisphere regions predicts anomia severity in aphasia. *Cereb Cortex*. 2010; 20(5):1013–1019. doi:bhp160 [pii]. 10.1093/cercor/bhp160 [PubMed: 19687294]
- Fridriksson J, Richardson JD, Fillmore P, Cai B. Left hemisphere plasticity and aphasia recovery. *Neuroimage*. 2012; 60(2):854–863.10.1016/j.neuroimage.2011.12.057 [PubMed: 22227052]
- Friederici AD, Kotz SA. The brain basis of syntactic processes: functional imaging and lesion studies. *Neuroimage*. 2003; 20(Suppl 1):S8–17. [PubMed: 14597292]
- Friston, K.; Ashburner, J.; Heather, J.; Holmes, A.; Poline, J. SPM8: Statistical Parametric Mapping (Version 8). 2009.
- Gelman A, Hill JC, Yajima M. Why We (Usually) Don't Have to Worry About Multiple Comparisons. *Journal of Research on Educational Effectiveness*. 2012; 5(2):189–211.

- Geranmayeh F, Brownsett SL, Wise RJ. Task-induced brain activity in aphasic stroke patients: what is driving recovery? *Brain*. 2014; 137(Pt 10):2632–2648.10.1093/brain/awu163 [PubMed: 24974382]
- Geva S, Baron JC, Jones PS, Price CJ, Warburton EA. A comparison of VLSM and VBM in a cohort of patients with post-stroke aphasia. *Neuroimage Clin*. 2012; 1(1):37–47.10.1016/j.nicl.2012.08.003 [PubMed: 24179735]
- Goldstein, H. Multilevel Statistical Models. 4th ed. John Wiley & Sons, Ltd; 2010.
- Gow DW Jr. The cortical organization of lexical knowledge: a dual lexicon model of spoken language processing. *Brain Lang*. 2012; 121(3):273–288.10.1016/j.bandl.2012.03.005 [PubMed: 22498237]
- Grafman J. Conceptualizing functional neuroplasticity. *J Commun Disord*. 2000; 33(4):345–355. quiz 355-346. [PubMed: 11001161]
- Heiss WD, Kessler J, Thiel A, Ghaemi M, Karbe H. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. *Ann Neurol*. 1999; 45(4):430–438. [PubMed: 10211466]
- Helm-Estabrooks, N. Cognitive linguistic quick test. The Psychological Corporation; San Antonio, TX: 2001.
- Hillis AE, Barker PB, Wityk RJ, Aldrich EM, Restrepo L, Breese EL, Work M. Variability in subcortical aphasia is due to variable sites of cortical hypoperfusion. *Brain Lang*. 2004; 89(3):524–530.10.1016/j.bandl.2004.01.007 [PubMed: 15120543]
- Hillis AE, Caramazza A. Category-specific naming and comprehension impairment: a double dissociation. *Brain*. 1991; 114(Pt 5):2081–2094. [PubMed: 1933235]
- Hillis AE, Heidler J. Mechanisms of early aphasia recovery. 2002; 16:885–895. *Aphasiology*.
- Hillis AE, Wityk RJ, Barker PB, Beauchamp NJ, Gailloud P, Murphy K, Metter EJ. Subcortical aphasia and neglect in acute stroke: the role of cortical hypoperfusion. *Brain*. 2002; 125(Pt 5):1094–1104. [PubMed: 11960898]
- Howard, D.; Patterson, K. The pyramids and palm trees test. Thames Valley Test Company; Bury St. Edmunds: 1992.
- Jefferies E. The neural basis of semantic cognition: converging evidence from neuropsychology, neuroimaging and TMS. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2013; 49(3):611–625.10.1016/j.cortex.2012.10.008
- Jefferies E. The neural basis of semantic cognition: Converging evidence from neuropsychology, neuroimaging and TMS. *Cortex*. 2013; (49):611–625. [PubMed: 23260615]
- Jordan LC, Hillis AE. Aphasia and right hemisphere syndromes in stroke. *Curr Neurol Neurosci Rep*. 2005; 5(6):458–464. [PubMed: 16263057]
- Kaplan, E.; Goodglass, H.; Weintraub, S. Boston Naming Test. Version 2nd Edition. Lippincott Williams & Wilkins; Philadelphia: 2001. Retrieved from <http://www.lib.utexas.edu:2048/login?url=http://www.lib.utexas.edu:2048/login?url=>
- Karbe H, Thiel A, Weber-Luxemburger G, Herholz K, Kessler J, Heiss WD. Brain plasticity in poststroke aphasia: what is the contribution of the right hemisphere? *Brain Lang*. 1998; 64(2):215–230.10.1006/brln.1998.1961 [PubMed: 9710490]
- Kertesz, A. The Western Aphasia battery. Grune & Stratton; Philadelphia, PA: 1982.
- Kim MJ, Jeon HA, Lee KM. Impairments of syntactic comprehension in Korean and the location of ischemic stroke lesions: a voxel-based lesion-symptom mapping study. *Behav Neurol*. 2010; 22(1-2):3–10.10.3233/BEN-2009-0254 [PubMed: 20543453]
- Kiran S, Meier EL, Kapse KJ, Glynn PA. Changes in task-based effective connectivity in language networks following rehabilitation in post-stroke patients with aphasia. *Front Hum Neurosci*. 2015; 9:316.10.3389/fnhum.2015.00316 [PubMed: 26106314]
- Lambon Ralph MA, Ehsan S, Baker GA, Rogers TT. Semantic memory is impaired in patients with unilateral anterior temporal lobe resection for temporal lobe epilepsy. *Brain : a journal of neurology*. 2012; 135(Pt 1):242–258.10.1093/brain/awr325 [PubMed: 22287382]
- Magnusdottir S, Fillmore P, den Ouden DB, Hjaltason H, Rorden C, Kjartansson O, Fridriksson J. Damage to left anterior temporal cortex predicts impairment of complex syntactic processing: a lesion-symptom mapping study. *Hum Brain Mapp*. 2013; 34(10):2715–2723.10.1002/hbm.22096 [PubMed: 22522937]

- Meinzer M, Beeson PM, Cappa S, Crinion J, Kiran S, Saur D, Thompson CK. Neuroimaging in aphasia treatment research: Consensus and practical guidelines for data analysis. *Neuroimage*. 2013 (0). 10.1016/j.neuroimage.2012.02.058
- Newman SD, Just MA, Keller TA, Roth J, Carpenter PA. Differential effects of syntactic and semantic processing on the subregions of Broca's area. *Brain Res Cogn Brain Res*. 2003; 16(2):297–307. S0926641002002859 [pii]. [PubMed: 12668239]
- Novick JM, Kan IP, Trueswell JC, Thompson-Schill SL. A case for conflict across multiple domains: memory and language impairments following damage to ventrolateral prefrontal cortex. *Cogn Neuropsychol*. 2009; 26(6):527–567.10.1080/02643290903519367 [PubMed: 20183014]
- Pillai JJ, Araque JM, Allison JD, Sethuraman S, Loring DW, Thiruvaiyaru D, Lavin T. Functional MRI study of semantic and phonological language processing in bilingual subjects: preliminary findings. *Neuroimage*. 2003; 19(3):565–576. [PubMed: 12880788]
- Piras F, Marangolo P. Noun-verb naming in aphasia: a voxel-based lesion-symptom mapping study. *Neuroreport*. 2007; 18(14):1455–1458.10.1097/WNR.0b013e3282ef6fc9 [PubMed: 17712273]
- Piras F, Marangolo P. When “Crack walnuts” lies in different brain regions: evidence from a voxel-based lesion-symptom mapping study. *J Int Neuropsychol Soc*. 2010; 16(3):433–442.10.1017/S1355617710000068 [PubMed: 20178682]
- Poldrack RA. Region of interest analysis for fMRI. *Soc Cogn Affect Neurosci*. 2007; 2(1):67–70.10.1093/scan/nsm006 [PubMed: 18985121]
- Price CJ. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage*. 2012; 62(2):816–847.10.1016/j.neuroimage.2012.04.062 [PubMed: 22584224]
- Price CJ, Warburton EA, Moore CJ, Frackowiak RS, Friston KJ. Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. *Journal of Cognitive Neuroscience*. 2001; 13(4):419–429. [PubMed: 11388916]
- Rapp AM, Mutschler DE, Erb M. Where in the brain is nonliteral language? A coordinate-based meta-analysis of functional magnetic resonance imaging studies. *Neuroimage*. 2012; 63(1):600–610.10.1016/j.neuroimage.2012.06.022 [PubMed: 22759997]
- Rastle K, Harrington J, Coltheart M. 358,534 nonwords: the ARC Nonword Database. *Q J Exp Psychol A*. 2002; 55(4):1339–1362.10.1080/02724980244000099 [PubMed: 12420998]
- Rehm K, Schaper K, Anderson J, Woods R, Stoltzner S, Rottenberg D. Putting our heads together: a consensus approach to brain/non-brain segmentation in T1-weighted MR volumes. *Neuroimage*. 2004; 22(3):1262–1270.10.1016/j.neuroimage.2004.03.011 [PubMed: 15219598]
- Reilly J, Rodriguez AD, Peelle JE, Grossman M. Frontal lobe damage impairs process and content in semantic memory: evidence from category-specific effects in progressive non-fluent aphasia. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2011; 47(6):645–658.10.1016/j.cortex.2010.05.005
- Reineck LA, Agarwal S, Hillis AE. “Diffusion-clinical mismatch” is associated with potential for early recovery of aphasia. *Neurology*. 2005; 64(5):828–833.10.1212/01.WNL.0000152983.52869.51 [PubMed: 15753418]
- Rorden, C. *MRICron*. 2012.
- Ruff I, Blumstein SE, Myers EB, Hutchison E. Recruitment of anterior and posterior structures in lexical-semantic processing: an fMRI study comparing implicit and explicit tasks. *Brain Lang*. 2008; 105(1):41–49. doi:S0093-934X(08)00004-7 [pii]. 10.1016/j.bandl.2008.01.003 [PubMed: 18279947]
- Sandberg CW, Bohland JW, Kiran S. Changes in functional connectivity related to direct training and generalization effects of a word finding treatment in chronic aphasia. *Brain Lang*. 2015; 150:103–116.10.1016/j.bandl.2015.09.002 [PubMed: 26398158]
- Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, Weiller C. Dynamics of language reorganization after stroke. *Brain*. 2006; 129(Pt 6):1371–1384. [PubMed: 16638796]
- Sebastian R, Kiran S. Task-modulated neural activation patterns in chronic stroke patients with aphasia. 2011; 25:927–951. *Aphasiology*.
- Stuss DT, Alexander MP. Is there a dysexecutive syndrome? *Philos Trans R Soc Lond B Biol Sci*. 2007; 362(1481):901–915.10.1098/rstb.2007.2096 [PubMed: 17412679]

- Thiel A, Hartmann A, Rubi-Fessen I, Anglade C, Kracht L, Weiduschat N, Heiss WD. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. *Stroke*. 2013; 44(8):2240–2246.10.1161/STROKEAHA.111.000574 [PubMed: 23813984]
- Thompson-Schill SL, Aguirre GK, D'Esposito M, Farah MJ. A neural basis for category and modality specificity of semantic knowledge. *Neuropsychologia*. 1999; 37(6):671–676. [PubMed: 10390028]
- Turkeltaub PE, Messing S, Norise C, Hamilton RH. Are networks for residual language function and recovery consistent across aphasic patients? *Neurology*. 2011; 76(20):1726–1734.10.1212/WNL.0b013e31821a44c1 [PubMed: 21576689]
- van Oers CA, Vink M, van Zandvoort MJ, van der Worp HB, de Haan EH, Kappelle LJ, Dijkhuizen RM. Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. *Neuroimage*. 2010; 49(1):885–893.10.1016/j.neuroimage.2009.08.057 [PubMed: 19733673]
- Vanderwouden, T. Celex - Building a Multifunctional, Polytheoretical Lexical Database. Paper presented at the Budalex '88 Proceedings; BUDAPEST, HUNGARY. 1990. <Go to ISI>://A1990BU59U00039
- Vartanian O. Dissociable neural systems for analogy and metaphor: implications for the neuroscience of creativity. *Br J Psychol*. 2012; 103(3):302–316.10.1111/j.2044-8295.2011.02073.x [PubMed: 22804698]
- Vigneau M, Beaucoisin V, Herve PY, Duffau H, Crivello F, Houde O, Tzourio-Mazoyer N. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage*. 2006; 30(4):1414–1432.10.1016/j.neuroimage.2005.11.002 [PubMed: 16413796]
- Walker GM, Schwartz MF, Kimberg DY, Faseyitan O, Brecher A, Dell GS, Coslett HB. Support for anterior temporal involvement in semantic error production in aphasia: new evidence from VLSM. *Brain Lang*. 2011; 117(3):110–122.10.1016/j.bandl.2010.09.008 [PubMed: 20961612]
- Wang Y, Holland SK. Comparison of Functional Network Connectivity for passive-listening and active-response narrative comprehension in adolescents. *Brain Connect*. 201410.1089/brain.2013.0190
- Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD. The right inferior frontal gyrus and poststroke aphasia: a follow-up investigation. *Stroke*. 2007; 38(4):1286–1292. [PubMed: 17322084]

Figure 1.
Lesion overlap (n = 14)

Figure 2.

Correlations between spared tissue and signal change. This diagram summarizes the spared to signal correlations for PWA. The region that an arrow originates from is the percent spared tissue region; the region that the arrow terminates at is the region showing signal change. Note label for positive versus negative correlations.

Figure 3. Signal correlations across regions. This diagram summarizes signal-to-signal correlations across regions, both for normal controls and for PWA. Note labels for positive versus negative correlations.

Table 1

Regions of interest and their presumed functions

Here presumed functions of this paper's selected ROIs are provided, based on prior literature as listed in the citations column.

Region	Presumed Function	Citations
Inferior Frontal Gyrus – Pars Orbitalis (IFGorb)	Semantic Processing	(Binder et al., 2009; Bookheimer, 2002; Fiez, 1997; Jeffries, 2013)
Inferior Frontal Gyrus – Pars Opercularis (IFGop)	Semantic Processing	(Pillai et al., 2003; Vigneau et al., 2006)
Inferior Frontal Gyrus – Pars Triangularis (IFGtri)	Semantic Cognition	(Jeffries, 2013; Vigneau et al., 2006)
Inferior Frontal Gyrus – Overall (IFG)	Phonological, working memory, and syntactic processes	(Binder et al., 2009)
	Semantic Processing	(Bedny, Hulbert, & Thompson-Schill, 2007; Binder et al., 2009; Cappa, 2012; Novick, Kan, Trueswell, & Thompson-Schill, 2009; Reilly, Rodriguez, Peelle, & Grossman, 2011; Ruff et al., 2008)
	Nonliteral Processing	(Benedek et al., 2014; Bohrn, Altmann, & Jacobs, 2012; Rapp, Mutschler, & Erb, 2012; Vartanian, 2012)
Superior Frontal Gyrus (SFG)	Semantic Processing	(Binder et al., 2009)
	Nonliteral Processing	(Benedek et al., 2014; Bohrn, Altmann, & Jacobs, 2012; Rapp, Mutschler, & Erb, 2012; Vartanian, 2012)
	Semantic Processing	(Binder et al., 2009; Pillai et al., 2003)
Middle Frontal Gyrus (MFG)	Language Processing	(Axelrod, Bar, Rees, & Yovel, 2014)
	Domain general activation with increased difficulty	(Fedorenko et al., 2013)
	Nonliteral Processing	(Benedek et al., 2014; Bohrn, Altmann, & Jacobs, 2012; Rapp, Mutschler, & Erb, 2012; Vartanian, 2012)
	Semantic Processing	(Binder et al., 2009; Cappa, 2012)
Middle Temporal Gyrus (MTG)	Language comprehension and semantic processing	(Chertkow, Bub, Deaudon, & Whitehead, 1997; Dronkers et al., 2004; Gow, 2012; Hillis & Caramazza, 1991; Kertesz, 1982)
	Semantic Processing	(Binder et al., 2009)
Angular Gyrus (AG)	Integration of individual concepts into a whole	(Friederici & Kotz, 2003; Newman, Just, Keller, Roth, & Carpenter, 2003)
Supramarginal Gyrus (SMG)	Semantic Processing	(Binder et al., 2009)
	Reading	(Booth et al., 2002; Gow, 2012)
Anterior Cingulate (ACC)	Language Control	(Abutalebi et al., 2008; Abutalebi, Rosa, Tettamanti, Green, & Cappa, 2009)
	Attention/Working Memory	(Wang & Holland, 2014)

Table 2

Participant information

Participant demographic and testing information is summarized in this table. Aphasia Quotient and Syndromic Diagnosis are provided by WAB. The scores from the *CLQT* provide composite severity.

ID	Gender	Age	Time Post-Stroke	Aphasia/Stroke Description	Aphasia Quotient	BNT	PAPT	CLQT	Experiment
1	M	60;4	13;6	Wernicke's or Conduction	71.2	36 (60%)	49 (94.23%)	Mild	1
2	M	59;3	2;0	Anomic or Transcortical Motor	78.6	50 (66.7%)	49 (94.23%)	WNL	2
3	M	55;9	6;5	Conduction	77.7	52 (86.7%)	51 (98.08%)	WNL	2
4	M	47;6	3;9	Anomic	95.5	57 (95%)	51 (98.08%)	WNL	2
5	M	53;0	9;3	Broca's	48	4 (6.7%)	45 (86.54%)	Mild	1
6	M	66;11	6;7	Broca's	49.6	9 (15%)	50 (96.15%)	Mild	1
7	M	48;5	7;10	Broca's or Conduction	72.5	49 (81.7%)	47 (90.38%)	Mild	2
8	F	66;9	1;8	Transcortical Motor	82.2	50 (83.3%)	39 (75%)	Severe	1
9	F	57;2	3;7	N/A**	99.2	55 (91.7%)	50 (96.15%)	WNL	2
10	M	69;2	1;4	Anomic	97.1	57 (95%)	51 (98.1%)	Mild	2
11	M	66;1	2;2	Anomic	97.2	39 (65%)	48 (92.31%)	Mild	1
12	M	74;6	11 months	Transcortical Motor	67.4	55 (91.7%)	48 (92.31%)	Mild	2
13	F	55;1	6 months	Anomic	84.7	54 (90%)	51 (98.1%)	WNL	2
14	F	63;1	8;2	Conduction	53.4	9 (15%)	50 (96.15%)	Mild	1
AVERAGES									
	75% M	59;7	5;11	--	76.6	40 (68%)	49 (90.74%)	--	50-50

Table 3
Percent spared tissue in ROIs in the left hemisphere for each participant

The numbers in the following table represent the percent spared tissue within each region for each participant. Darker shading implies greater damage, and thus less percent spared.

Participants																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Averages	
Regions	LIFGop	21	3	46	51	45	94	4	36	6	100	95	41	56	38	45
	LIFGorb	46	93	85	85	80	81	31	100	88	100	100	100	97	34	80
	LIFGtri	28	10	85	73	72	99	13	78	48	100	100	78	70	68	66
	LMFG	78	55	62	99	82	100	66	58	90	100	100	61	99	99	82
	LSFG	99	98	99	100	92	100	85	89	100	100	100	64	100	100	96
	LMTG	5	72	13	86	37	1	5	99	96	99	100	100	87	1	57
	LAG/SMG	14	31	75	78	1	58	1	63	59	88	100	100	73	4	53
	LACC	96	100	100	100	93	100	99	97	100	100	100	82	100	100	98

Table 4

Principal components analysis factors

Percentage values for each factor reflect the individual percent variation explained by that factor; scores of interest are marked in bold and shaded boxes.² Together, these factors explain 79.6% of the variance.

		Factor 1 Positive: Traditional Language Regions Negative: Compensatory Regions 38.2%	Factor 2 Traditional Language Regions 17.5%	Factor 3 Positive: Semantic Processing Regions 12.2%	Factor 4: Semantic Processing Regions 11.4%
Amount of spared tissue	LIFGop percent spared	0.42	0.66	-0.19	0.28
	LIFGorb percent spared	0.64	-0.01	-0.63	0.07
	LIFGtri percent spared	0.63	0.64	-0.07	0.24
	LMFG percent spared	0.08	0.65	-0.16	0.43
	LSFG percent spared	-0.62	0.43	-0.36	0.43
	LMTG percent spared	0.61	-0.08	-0.58	-0.14
	LAG/SMG percent spared	0.72	0.20	-0.37	0.14
	LACC percent spared	-0.59	0.48	-0.45	0.21
Ipsilesional BOLD Signal Change	LIFGop signal change	-0.61	-0.43	-0.46	0.39
	LIFGorb signal change	-0.34	-0.44	0.37	0.57
	LIFGtri signal change	-0.45	-0.58	0.01	0.57
	LMFG signal change	-0.85	-0.07	0.07	0.24
	LSFG signal change	-0.76	0.19	0.27	0.31
	LMTG signal change	-0.33	0.21	0.15	0.73
	LAG/SMG signal change	-0.30	0.27	0.66	-0.01
	LACC signal change	-0.48	0.66	0.34	-0.32
Contralesional BOLD Signal Change	RIFGop signal change	-0.86	0.08	-0.38	-0.18
	RIFGorb signal change	-0.03	0.84	0.31	-0.17
	RIFGtri signal change	-0.84	-0.08	-0.33	-0.07
	RMFG signal change	-0.82	0.20	-0.47	-0.22
	RSFG signal change	-0.83	0.23	-0.20	-0.21
	RMTG signal change	-0.71	-0.20	0.08	-0.20

²Of note, some structures scored greater than 0.5 in multiple factors. In these cases we assigned structures to the factor for which they had the highest score.

		Factor 1 Positive: Traditional Language Regions Negative: Compensatory Regions 38.2%	Factor 2 Traditional Language Regions 17.5%	Factor 3 Positive: Semantic Processing Regions 12.2%	Factor 4: Semantic Processing Regions 11.4%
	RAG/SMG signal change	-0.63	-0.29	-0.21	-0.54
	RACC signal change	-0.68	0.49	0.01	-0.28
Accuracy	Experimental Task	-0.40	0.08	-0.18	0.61
	Accuracy*				
	Control Condition Accuracy*	-0.54	0.19	-0.12	0.29

* supplemental factor

Table 5
Significant percent spared to percent signal change correlations with task as a covariate

Positive correlations indicate that the less percent spared, the less the signal change (more damage, less signal). *Negative correlations* indicate that the more percent spared, the less the signal change (more damage, more signal). A legend is provided relating each region to factors from the PCA analysis; additionally, a scale is given explaining the heat map design of the table. Numbers bolded are significant corrected for multiple comparison.

Predictor	LIFGtri % signal	LIFGop % signal	RIFGop % signal	RIFGtri % signal	LIFGorb % signal	RMTG % signal	RAG/SMG % signal	RIFGorb % signal	LMTG % signal	RMFG % signal	LAG/SMG % signal	LMFG % signal	RSFG % signal	RACC % signal	LSFG % signal	LACC % signal
LACC % spared	3.02	2.98	2.86	2.83	2.83	2.77	2.72	2.66	2.64	2.69	2.54	2.57	2.56	2.51	2.50	2.38
LSFG % spared	3.87	3.81	3.53	3.50	3.48	3.33	3.21	3.09	3.08	3.18	2.85	2.92	2.89	2.79	2.77	2.51
LMFG % spared	0.84	0.69	0.34	0.22	0.20	0.07	-0.17	-0.17	-0.25	-0.21	-0.62	-0.59	-0.61	-0.75	-0.80	-1.17
LIFGop % spared	0.32	0.26	0.09	-0.27	-0.69	-0.55	-0.78	-0.65	-0.80	-0.86	-1.82	-1.64	-1.64	-1.65	-1.80	-2.65
LIFGtri % spared	-0.93	-0.60	-1.12	-1.55	-1.77	-1.40	-1.73	-2.05	-2.08	-2.07	-3.13	-2.62	-2.60	-2.66	-2.80	-4.11
LIFGorb % spared	-0.69	-0.80	-1.56	-1.74	-1.77	-1.83	-2.07	-2.38	-2.38	-2.34	-3.07	-2.92	-2.91	-3.07	-3.22	-3.85
LMTG % spared	0.05	0.09	-0.69	-1.09	-1.14	-0.89	-1.16	-1.64	-1.57	-1.74	-2.73	-2.88	-2.49	-2.60	-3.26	-3.82
LAG/SMG % spared	-0.12	-0.39	-1.23	-1.67	-1.60	-1.24	-1.66	-1.81	-1.85	-2.28	-2.82	-2.91	-2.88	-2.85	-3.20	-4.12

Table 6
Significant correlations of signal change across regions with task as a covariate for (A) controls and (B) patients

Within this table, each region is listed with its significant correlations with other regions, controlling for task. A scale is given explaining the heat map design of the table. Numbers bolded are significant.

A	LIFGop	RIFGop	LIFGorb	RIFGorb	LIFGtri	RIFGtri	LMFG	RMFG	LSFG	RSFG	LMTG	RMTG	LAG/SMG	RAG/SMG	LACC	RACC
LIFGop	1.00	0.66	0.78	0.72	0.89	0.35	0.86	0.47	0.61	0.28	0.33	0.41	0.81	0.25	0.70	0.62
RIFGop	0.66	1.00	0.66	0.64	0.77	0.58	0.50	0.42	-0.04	0.05	0.27	0.31	0.47	0.43	0.40	0.17
LIFGorb	0.78	0.66	1.00	0.94	0.92	0.49	0.83	0.64	0.57	0.55	0.53	0.64	0.86	0.55	0.92	0.72
RIFGorb	0.72	0.64	0.94	1.00	0.84	0.52	0.82	0.68	0.59	0.73	0.75	0.82	0.87	0.77	0.81	0.62
LIFGtri	0.89	0.77	0.92	0.84	1.00	0.65	0.91	0.57	0.42	0.35	0.32	0.41	0.73	0.40	0.85	0.72
RIFGtri	0.35	0.58	0.49	0.52	0.65	1.00	0.51	0.62	-0.20	0.34	0.07	0.14	0.11	0.41	0.46	0.30
LMFG	0.86	0.50	0.83	0.82	0.91	0.51	1.00	0.42	0.63	0.48	0.44	0.45	0.74	0.45	0.86	0.88
RMFG	0.47	0.42	0.64	0.68	0.57	0.62	0.42	1.00	0.32	0.71	0.37	0.61	0.56	0.45	0.54	0.19
LSFG	0.61	-0.04	0.57	0.59	0.42	-0.20	0.63	0.32	1.00	0.60	0.59	0.64	0.85	0.28	0.62	0.64
RSFG	0.28	0.05	0.55	0.73	0.35	0.34	0.48	0.71	0.60	1.00	0.79	0.87	0.61	0.77	0.50	0.36
LMTG	0.33	0.27	0.53	0.75	0.32	0.07	0.44	0.37	0.59	0.79	1.00	0.95	0.70	0.91	0.34	0.25
RMTG	0.41	0.31	0.64	0.82	0.41	0.14	0.45	0.61	0.64	0.87	0.95	1.00	0.80	0.85	0.45	0.25
LAG/SMG	0.81	0.47	0.86	0.87	0.73	0.11	0.74	0.56	0.85	0.61	0.70	0.80	1.00	0.52	0.75	0.60
RAG/SMG	0.25	0.43	0.55	0.77	0.40	0.41	0.45	0.45	0.28	0.77	0.91	0.85			0.35	0.22
LACC	0.70	0.40	0.92	0.81	0.85	0.46	0.86	0.54	0.62	0.50	0.34	0.45	0.75	0.35	1.00	0.89
RACC	0.62	0.17	0.72	0.62	0.72	0.30	0.88	0.19	0.64	0.36	0.25	0.25	0.60	0.22	0.89	1.00

B	LIFGop	RIFGop	LIFGorb	RIFGorb	LIFGtri	RIFGtri	LMFG	RMFG	LSFG	RSFG	LMTG	RMTG	LAG/SMG	RAG/SMG	LACC	RACC
LIFGop	1.00	0.55	0.36	-0.53	0.74	0.62	0.62	0.54	0.42	0.43	0.32	0.41	-0.42	0.42	-0.26	0.01
RIFGop	0.55	1.00	0.08	-0.08	0.26	0.92	0.63	0.93	0.49	0.77	0.05	0.52	0.12	0.80	0.40	0.66
LIFGorb	0.36	0.08	1.00	-0.44	0.61	0.27	0.20	-0.13	0.18	-0.22	0.48	0.16	0.28	0.10	-0.17	-0.17
RIFGorb	-0.53	-0.08	-0.44	1.00	-0.70	-0.12	-0.13	0.11	0.13	0.16	0.15	0.04	0.32	-0.28	0.73	0.41
LIFGtri	0.74	0.26	0.61	-0.70	1.00	0.45	0.59	0.17	0.23	0.03	0.23	0.30	-0.05	0.27	-0.47	-0.17
RIFGtri	0.62	0.92	0.27	-0.12	0.45	1.00	0.66	0.88	0.45	0.62	0.13	0.54	0.10	0.75	0.30	0.51
LMFG	0.62	0.63	0.20	-0.13	0.59	0.66	1.00	0.70	0.82	0.74	0.21	0.66	0.13	0.45	0.19	0.58

B	LIFGop	RIFGop	LIFGorb	RIFGorb	LIFGtri	RIFGtri	LMFG	RMFG	LSFG	RSFG	LMTG	RMTG	LAG/SMG	RAG/SMG	LACC	RACC
RMFG	0.54	0.93	-0.13	0.11	0.17	0.88	0.70	1.00	0.55	0.87	0.08	0.56	0.00	0.68	0.43	0.73
LSFG	0.42	0.49	0.18	0.13	0.23	0.45	0.82	0.55	1.00	0.69	0.29	0.51	0.17	0.28	0.50	0.61
RSFG	0.43	0.77	-0.22	0.16	0.03	0.62	0.74	0.87	0.69	1.00	0.12	0.67	0.03	0.58	0.46	0.81
LMTG	0.32	0.05	0.48	0.15	0.23	0.13	0.21	0.08	0.29	0.12	1.00	0.25	0.18	-0.27	0.11	0.15
RMTG	0.41	0.52	0.16	0.04	0.30	0.54	0.66	0.56	0.51	0.67	0.25	1.00	0.17	0.50	0.28	0.37
LAG/SMG	-0.42	0.12	0.28	0.32	-0.05	0.10	0.13	0.00	0.17	0.03	0.18	0.17	1.00	0.16	0.55	0.45
RAG/SMG	0.42	0.80	0.10	-0.28	0.27	0.75	0.45	0.68	0.28	0.58	-0.27	0.50	0.16	1.00	0.30	0.43
LACC	-0.26	0.40	-0.17	0.73	-0.47	0.30	0.19	0.43	0.50	0.46	0.11	0.28	0.55	0.30	1.00	0.70
RACC	0.01	0.66	-0.17	0.41	-0.17	0.51	0.58	0.73	0.61	0.81	0.15	0.37	0.45	0.43	0.70	1.00

1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0	-0.1	-0.2	-0.3	-0.4	-0.5	-0.6	-0.7	-0.8	-0.9	-1
---	-----	-----	-----	-----	-----	-----	-----	-----	-----	---	------	------	------	------	------	------	------	------	------	----