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Running Head: WORD READING IN APHASIA

The Neural Basis of Successful Word Reading in Aphasia

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ABSTRACT

Objective: Understanding the neural basis of recovery from stroke is a major research goal. Many functional neuroimaging studies have identified changes in brain activity in people with aphasia, but it is unclear whether these changes truly support successful performance or merely reflect increased task difficulty. We addressed this problem by examining differences in brain activity associated with correct and incorrect responses on an overt reading task. Based on previous proposals that semantic retrieval can assist pronunciation of written words, we hypothesized that recruitment of semantic areas would be greater on successful trials.

Methods: Participants were 21 left hemisphere stroke patients with phonologic retrieval deficits. They read words aloud during an event-related fMRI paradigm. Blood oxygen-level dependent (BOLD) signals obtained during correct and incorrect trials were contrasted to highlight brain activity specific to successful trials.

Results: Successful word reading was associated with higher BOLD signal in the left angular gyrus. In contrast, BOLD signal in bilateral posterior inferior frontal cortex, supplementary motor area, and anterior cingulate cortex was greater on incorrect trials.

Interpretation: These data show for the first time the brain regions where neural activity is correlated specifically with successful performance in people with aphasia. The angular gyrus is a key node in the semantic network, consistent with the hypothesis that additional recruitment of the semantic system contributes to successful word production when phonologic retrieval is impaired. Higher activity in other brain regions during incorrect trials likely reflects secondary engagement of attention, working memory, and error monitoring processes when phonologic retrieval is unsuccessful.

Keywords: reading, aphasia, fMRI, phonology, semantics

INTRODUCTION

Recovery of language functions after brain damage is often assumed to involve a degree of reorganization of neural processing, but this recovery mechanism is still not well understood. Despite a large number of functional neuroimaging studies documenting perilesional and contralesional activation in patients with aphasia during language tasks (e.g., Crosson et al., 2007; Fridriksson, Baker, & Moser, 2009; Hamilton, Chrysikou, & Coslett, 2011; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Mohr et al., 2016; Saur et al., 2006; Thompson & den Ouden, 2008), there is continued debate about the nature of this activation and how it contributes to recovery (Crosson et al., 2007; Fridriksson, Richardson, Fillmore, & Cai, 2012; Gainotti, 2015; Geranmayeh, Brownsett, & Wise, 2014; Hillis, 2005; Lee, Zreik, & Hamilton, 2017; Price & Crinion, 2005; Turkeltaub et al., 2012). An inherent confounding factor in such studies is that the tasks used are likely to be more difficult for patients with brain damage than for healthy controls, therefore any additional activation in patients might simply reflect additional effort or recruitment of attention and working memory resources (Geranmayeh et al., 2014). Furthermore, it is unclear whether such recruitment necessarily improves performance, and there is even evidence that such activation can be a marker of poorer recovery (Martin et al., 2009; Naeser et al., 2004; Postman-Caucheteux et al., 2010; Rosen et al., 2000).

To address more directly the question of how neural activity enhances performance after stroke, we asked whether activation in patients is directly correlated with improved performance. Recovery of language after stroke is almost never an all-or-none phenomenon; instead, patients typically show partial recovery characterized by variable degrees of success across a set of trials. This trial-to-trial variability makes it possible to examine patterns of neural activity that are uniquely associated with correct and incorrect responses.

Performance-correlated brain activity has been explored only rarely in patients with aphasia. Fridriksson and colleagues (2009) compared fMRI signals during correct and incorrect responses on a picture naming task in 11 patients with aphasia. Although qualitative differences were reported between the correct and incorrect trial activation maps obtained from contrasts with a low-level sensory control, no significant differences emerged when correct and incorrect responses were directly contrasted. This null result suggests that any difference in activation between correct and incorrect responses may be subtle. In addition, the sample of aphasia patients examined was small and had heterogenous behavioral profiles, thus power was likely reduced for finding a significant result (Fridriksson et al., 2009). Postman-Caucheteux et al. (2010) studied 3 patients with fMRI during picture naming, using a similar event-related analysis to compare activation during correct and incorrect responses. The authors observed relatively greater right frontal activation during incorrect responses, but no consistent areas of greater activation during correct trials. Lee et al. (2017) compared correct and incorrect trials during picture naming in a single patient with semantic deficits. In contrast to the right frontal activation reported by Postman-Caucheteux, error trials were associated with greater activation in the right superior temporal sulcus and supramarginal gyrus (Lee et al., 2017). Similar to the Postman-Caucheteux results, no areas showed greater activation during correct responses. These results are all in direct contrast to a single case study by Meinzer et al. (2006), who showed that correct responses on a similar picture naming task were associated with greater right frontal activation compared to incorrect responses.

The present study uses an overt word reading task to assess performance-correlated brain activity. We reasoned that this task might be more sensitive than picture naming for detecting adaptive brain reorganization because of the availability of alternative processing strategies for phonologic retrieval in the case of words. Whereas picture naming cannot proceed without activation of the concept (semantic representation) that the picture represents, word pronunciation is thought to involve only partial or optional activation of a semantic representation (Graves et al., 2014; Plaut, McClelland, Seidenberg, & Patterson, 1996). Strokes affecting the middle cerebral artery (MCA) territory very often damage perisylvian phonological processing networks while leaving semantic systems relatively intact (Pillay, Stengel, Humphries, Book, & Binder, 2014; Rapcsak et al., 2009; Ripamonti et al., 2014). We hypothesized, therefore, that in stroke patients with primarily phonologic system damage, the relatively preserved semantic network might play a role in facilitating word pronunciation. In some well-supported theories of word pronunciation, activation of a word's meaning (semantic representation) is thought to provide additional information that can assist in retrieving a phonologic code (Plaut et al., 1996). Activation in undamaged regions of the semantic network (Binder, Desai, Graves, & Conant, 2009) was therefore predicted to be greater on trials in which pronunciation was successful compared to trials in which pronunciation was incorrect.

MATERIALS AND METHODS

Participants

Participants were 21 chronic left hemisphere ischemic stroke patients (10 women, 11 men) who demonstrated a residual phonologic retrieval deficit together with intact semantic processing. Participants were selected based on their behavioral deficit from a group of chronic aphasia patients enrolled prospectively in a larger study. All patients with this behavioral profile were eligible, regardless of where in the left hemisphere the lesion was located. To determine phonologic and semantic function, patients were tested on behavioral tasks (described below) prior to MRI scanning. Impaired phonologic processing was defined as a z-score less than -1.67 (critical value for bottom tail of distribution, $p = .05$) on a pseudoword rhyme matching task, and intact semantic processing was defined as a z-score greater than -1.67 on a semantic matching task. Raw scores were transformed to z-scores based on performance data from 24 healthy, right-handed, age- and education-matched controls (mean age = 57.7 years, mean education = 15 years).

All patients were at least 180 days post-stroke, native English speakers, and pre-morbidly right-handed according to the Edinburgh Handedness Inventory handedness quotient ($M = 84.0$, $SD = 25.9$) (Oldfield, 1971). Lesions included 17 MCA infarcts, 2 combined MCA/anterior cerebral artery infarcts, and 2 combined MCA/posterior cerebral artery infarcts. Demographic data for patients are listed in Table 1, and individual subject data are presented in Table 2. All patients provided written informed consent to participate and were enrolled prospectively under a protocol approved by the Medical College of Wisconsin Institutional Review Board and undertaken in accord with the Declaration of Helsinki.

Screening Language Assessment

Behavioral tasks were given to characterize key language abilities for inclusion in the study prior to fMRI scanning. The tasks were administered on a laptop computer connected to a touch-sensitive LCD monitor (ELO model 1522L) and programmed in the "LiveCode" environment (https://livecode.com). Testing occurred in a quiet clinic room. Participants initiated each trial by touching an empty green square on the computer screen.

To measure phonologic impairment, participants were asked to complete a 72-trial pseudoword rhyme matching task (Figure 1, left). On each trial, a sample pseudoword (e.g., *hoark*) was presented in the center of a computer display with two choice items (e.g., *lorque* and *rauke*) presented side by side below the sample. Subjects indicated via button press which of the two items rhymed with the sample. Trials were designed to take advantage of the fact that English has multiple possible spellings for the same sound (e.g., ***vair*** » ***plare***/*shar*), enabling decoupling of phonologic similarity from orthographic similarity. All items had unambiguous (i.e., highly consistent) pronunciations.

To assess semantic processing, participants completed a 120-trial semantic picture matching task, similar to the "Camel and Cactus" test (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000) (Figure 1, right). This task required participants to select from two choices the item that was most similar to the sample picture (i.e., ***eagle*** » *robin* vs. ***hawk***).

Patients also completed an 80-item picture-naming task described elsewhere (Pillay, Binder, Humphries, Gross, & Book, 2017). Results are provided in Table 2 to further characterize the aphasia severity in each patient, but were not used in the context of the present study and are not discussed further.

Functional Imaging

FMRI Tasks

Participants who met inclusion criteria on the language screening assessment then underwent an fMRI session, during which they performed an overt reading task with single words. Spoken responses were used because they allowed for definitive scoring of responses and classification of correct and incorrect trials. Participants read aloud 72 concrete nouns ranging in length from 4-6 characters. Imageability (ease of mental image retrieval, rated on a 1-7 scale (Cortese & Fugett, 2004) ranged from 3.66 to 6.43, M = 5.50. Written word frequency ranged from 8 to 260/million, M = 59/million (Baayen, Piepenbrock, & Gulikers, 1995). In addition to the reading trials, 72 fixation intervals were randomly dispersed among the trials to create a variable inter-stimulus interval for optimal fast event-related analysis.

Stimulus Presentation and Response Recording

Timing and order of stimulus presentation was controlled with E-prime software and synchronized to MRI data acquisition. Standard 800 x 600 pixel RGB output was sent from a PC to an LCD video projector. Images were back-projected on a screen located 240 cm from a prism lens mounted within the head coil just above the subject's eyes. Individual stimuli were presented in the center of a screen in white font on a black background and subtended a visual angle of 2.0-2.5°. Stimuli were presented for 2000 milliseconds and followed by a fixation cross until the next stimulus. The mean trial duration was 6.58 seconds.

Spoken responses were captured via a fiber-optic dual-channel noise-canceling microphone (FOMRI-III, Optoacoustics) positioned near the subject's mouth. Tones marking the onset of each trial (inaudible to the subject) were recorded on a second audio channel. Responses were then phonetically transcribed off-line for accuracy, response time, and error analyses. Responses were considered errors if the participant failed to produce a complete response or failed to produce a correct response. Incomplete or incorrect responses that were followed immediately by correct responses were counted as correct as long as the correct response occurred before the next trial. For completeness, error responses were also subclassified as omissions (i.e., no response or fragmentary utterance), phonologic paraphasias (i.e., phonologically related neologism or word), semantic paraphasias, or phonologically and semantically unrelated errors, though these error types were not separately analyzed in the fMRI analysis.

Word reading is often a challenging task for people with aphasia, and becomes more challenging when coupled with performing in an unfamiliar fMRI environment with constraints on available response time. Functional neuroimaging measurements are sensitive to response time, working memory, and attentional effort (Binder, Medler, Desai, Conant, & Liebenthal, 2005), and the use of an overt production task permits collection of response times for assessment of overall trial difficulty. A custom Matlab script was used to estimate RT, from stimulus onset to response onset, for each trial in each subject. Each auditory waveform and response onset marker was visually inspected for accuracy and manually adjusted as needed. These RT data were incorporated directly into the image analysis in an attempt to delineate brain areas modulated by task difficulty (Binder, Medler, et al., 2005). Two patients did not have RT data available due to error in collecting stimulus onset times, reducing the *n* to 19 for this additional analysis.

MRI Acquisition

All fMRI data were acquired at 3T using a GE Excite whole-body scanner. Four patients were scanned with a 32-channel head coil. The remaining participants were scanned with an 8-channel head coil. A gradient-echo, echo-planar imaging (EPI) sequence (flip angle = 77°, TE = 25 ms, TR = 2000 ms, NEX = 1, FOV = 192 cm, matrix = 64 x 64, slice thickness = 3 mm, inter-slice gap = 0.5 mm, 36 axial slices) was used for isotropic (3 x 3 x 3mm) whole-brain fMRI data acquisition. Head movement was monitored during scanning using real-time image registration. High resolution T1-weighted anatomical reference images were obtained using a spoiled gradient-recalled (SPGR) sequence (flip = 12°, TE = MinFull, T1 (prep) = 450 ms, TR = 8.2 ms, NEX = 1, voxels 1.0 x 1.0 x 1.0 mm, 162 axial slices).

Lesion Tracing and Template Registration

Lesioned areas were identified using a semi-automated procedure to create an individual lesion map for each patient (Pillay et al., 2014). Each patient's anatomical image and associated lesion map were then morphed to a stereotaxic template ("Colin N27") using 3dQwarp, a nonlinear registration routine in the Analysis of Functional NeuroImages (AFNI) software package (https://afni.nimh.nih.gov). The registration included constrained cost-function masking using the lesion volume as a mask, and resampling to a nominal 1x1x1 mm voxel grid. The parameters used for warping each individual’s anatomy to the template were then applied to the functional images. This nonlinear registration process corrects for anatomical distortions that are common after focal brain damage, particularly local ventricular enlargement. The group lesion overlap map is presented in Figure 2.

FMRI Data Analysis

Image processing and statistical analyses were performed using AFNI software. Preprocessing steps included slice timing correction and image registration. For each subject, the first four images in each time series were discarded prior to regression analysis to avoid saturation effects. Translation and rotation parameters, estimated during registration, were saved for use as noise covariates. EPI volumes were then registered to the T1 anatomical image using a modality-specific cost function based on weighted local Pearson coefficients (Saad et al., 2009) using the AFNI script "align_epi_anat.py". Images contaminated by large artifacts, such as motion, were detected automatically using regression techniques built into the AFNI program "3dToutcount" and censored from the analysis. No data sets required censoring of more than 10% of the images (mean percent censored = 3.78, SD = 2.11).

BOLD signal changes were analyzed with a multiple linear regression model using the AFNI program 3dDeconvolve. Stimulus regressors were created for each task condition, convolved with a canonical gamma variate hemodynamic response function. Six motion vectors computed during image registration were included as covariates of no interest, along with an additional covariate from signal in the ventricles to estimate speech movement artifact (Graves, Grabowski, Mehta, & Gordon, 2007). A Gaussian kernel of 5 mm FWHM was used for smoothing prior to the regression analysis.

Group Contrasts. The contrast of interest was between words that were read successfully and words that elicited errors (Correct - Error), which specifically identifies brain activity correlated with successful performance. Due to variable patient performance, and therefore unequal numbers of trials in each condition across patients, it was necessary to determine the lower limit of trials acceptable for subject inclusion in the analysis. As the number of trials for a particular condition (correct or incorrect) decreases, the reliability of the corresponding parameter estimate also decreases (i.e., the standard deviation of the estimate increases). Increasing the criterion for minimum trial number, however, reduces power at the group level because of the reduction in number of subjects who meet criteria. Model quality for a given combination of minimum trial number and group sample size can be determined by inverting the regressor matrix and taking the standard deviation of the resulting values. In formal terms, the linear regression model for this analysis is given by: $y = X\beta + \varepsilon$ where y = the measured response, X = the design matrix, β = vector of unknown parameters, and ε = measurement error. The least squares estimate of β is given by: $b = (X^1X)^{-1}X^1y$, and the variance of the parameter estimate is estimated by: $s^2(b) = MSE(X^1X)^{-1}$ where MSE is the mean square error, a scalar that estimates the error measurement variance. The standard deviation for a particular element of the b vector, $s(b_k)$, is given by the square root of the corresponding diagonal element of the $s^2(b)$ matrix. If the measurement variance is assumed to be constant across experimental designs, then $s^2(b)$ is a function of the structure of X alone, allowing computation of a normalized standard deviation (nSD) for each experimental design (i.e., each combination of minimum trial number criterion and resulting group sample size). Minimizing this nSD produces the most reliable final parameter estimates (Ward, 2006). Using this method, nSD was calculated by setting a minimum trial number criterion and using the observed distribution of trial numbers in the real data to determine the resulting group sample size. This procedure was repeated over a range of minimum trial number criteria. A minimum of 2 time points for subject inclusion was determined to be optimal for minimizing nSD and thus maximizing the reliability of the parameter estimates and power at the group level. Thus, patients were included in the analysis if they made at least 2 error responses.

The result of this simulation may seem surprising, given that a sample of 2 trials would be very unlikely to yield a reliable activation map at the individual subject level. The crucial point here is that there is a direct trade-off between minimum number of trials allowed and sample size at the group level. The simulation indicates that sample size at the group level has a much larger effect than power at the individual subject level on power at the group level. The majority of the sample (62%) made more than 10 error responses. Two patients made just 2 error responses, yet the simulation suggests that power at the group level is enhanced when these patients are included. To test this prediction, we repeated the main contrast between correct and incorrect trials but included only patients with at least 10 errors, which reduced the sample size to 13 patients. The results were similar, however, they did not survive significance, likely due to reduced power.

Patients were selected for inclusion if they had a phonologic access deficit and relatively preserved semantic store. We hypothesized that the preserved semantic network may play a role in facilitating word production (Plaut et al., 1996), and that activation in undamaged regions of the semantic network may be greater for correct trials than incorrect trials. The overlap between the thresholded Correct – Error activation map and semantic regions identified in a previous meta-analysis (Binder et al., 2009) was examined to determine whether patients engaged semantic regions more for correct than incorrect trials.

Two additional analyses were completed in an effort to reduce variance due to individual factors. In the first, the phonologic impairment z-score for each patient was included as a covariate to remove variation correlated with impairment severity. In theory, the severity of phonologic impairment might systematically modulate the degree of compensatory activation in undamaged brain regions, thus adding between-participant variance. Controlling for this factor might enhance detection of activation that is independent of severity level. In the second analysis, lesioned tissue was excluded on a voxel-wise basis from the group-level *t*-test. That is, the group-level *t*-test at each voxel included only the subset of patients who did not have a lesion involving the voxel. Presumably this reduces variance at each voxel resulting from the presence or absence of a lesion, which may improve sensitivity despite the smaller sample size at some voxels. This method results in the degrees of freedom varying across voxels, depending on the group level lesion burden (e.g., a voxel in the center of the left insula would have fewer degrees of freedom because it is more likely to be lesioned than a voxel in the left occipital lobe). Each voxel was thresholded, however, to the same alpha level ($p < .01$).

Finally, the RTs on each trial (including error trials) were included in a regression model, after normalization of the RT values, to account for variance due solely to time on task, a presumed marker of task difficulty. Separate RT maps were created for correct and incorrect conditions, and these maps were then combined within subjects so that the resulting RT map captured variance independent of condition. As there were different numbers of trials in each condition, within-subject RT maps were weighted by the number of trials per condition before being averaged.

All contrasts were first computed at the individual subject level. Beta coefficient maps for these contrast maps (registered to the common template space) were then analyzed with a single-sample *t*-test at the group level. Activation maps were thresholded at voxel-wise $p < .01$ and minimum cluster size of 1609 μl, corresponding to a whole brain $p < 0.05$. The whole brain probability was derived from Monte Carlo simulations using simulated data. Spatial smoothing was applied to the simulated data using a model composed of a Gaussian and mono-exponential function, which was fit to the residual dataset from the regression analysis (using 3dFWHMx in AFNI). The addition of the mono-exponential function to the Gaussian model was performed to address the increased false positive rates found when using a Gaussian model alone (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Eklund, Nichols, & Knutsson, 2016).

RESULTS

Task performance

Performance on the two behavioral measures completed outside the MRI environment are reported in Table 1. Across all patients, semantic matching performance (M = 93.8, SD = 1.7) was significantly better than pseudoword rhyme matching performance (M = 67.5, SD = 14.1), as prescribed by the inclusion criteria. Patients performed worse than controls on the pseudoword rhyme matching task ($t(37) = -7.89$, $p < .001$), but did not perform differently from controls on the semantic matching task, ($t(37) = -1.43$, $p = .16$).

Mean accuracy on the fMRI word reading task was 75.9% (SD = 20.4). The number of errors ranged from 2 (2.8%) to 52 (72.2%). Words read correctly were significantly more imageable (M = 5.56, SD = 0.06) than words read incorrectly (M = 5.14, SD = 0.28; $p < .001$). In addition, words read correctly had higher frequencies (M = 64.2, SD = 3.3) than words read incorrectly (M = 41.2, SD = 13.1; $p < .001$). The majority of errors were phonologically related to the target item (M = 10.4, SD = 8.2), followed by errors that were unrelated to the target item (M= 3.7, SD = 6.7). Semantically related errors were rare (M = 1.7, SD = 1.4), as were omissions (M= 1.4, SD = 2.2). Reading accuracy was not correlated with age, education, gender, or days-post-onset. Individual patient performances are shown in Table 2.

Mean RT on the reading task was 1291 ms (SD = 380) across all trials. Correct responses (M = 1228 ms, SD = 356) were faster than incorrect responses (M = 1362 ms, SD = 399), but this difference was not statistically significant (*p* = .469). Across participants, mean RT for correct trials was negatively correlated with reading accuracy (*r* = -.50, *p* = .03).

FMRI results

Stereotaxic coordinates of activation peaks are listed in Table 3. Areas that were differentially engaged during successful and unsuccessful reading are shown in Figure 3A. The left angular gyrus (AG) was more active for correct word trials (Correct > Error). In contrast, four regions were more active for incorrect word trials (Error > Correct). The largest of these were located bilaterally in the supplementary motor area (SMA) and dorsal anterior cingulate gyrus. The other two clusters involved similar regions in the right and left posterior inferior frontal cortex, extending from the inferior precentral gyrus to the pars opercularis of the inferior frontal gyrus (IFG). On the right side this cluster extended farther ventrally into the anterior insula.

Brain areas modulated by RT regardless of stimulus condition are shown in Figure 3B. Several regions identified in the Error > Correct contrast also showed positive correlations with time on task, including the SMA and dorsal anterior cingulate cortex bilaterally, the right posterior IFG and precentral gyrus, and the right anterior insula. Other areas modulated by RT included the right central sulcus, bilateral mid-cingulate and posterior cingulate gyrus, bilateral cuneus and lingual gyrus, and bilateral thalamus. No areas were negatively correlated with RT.

To assess the relationship between the left AG area activated during successful reading and areas previously identified with semantic processing, the Correct – Error activation map was overlapped with a meta-analysis map of regions activated by semantic contrasts in healthy participants (Binder et al., 2009). As shown in Figure 4, the left AG region associated with correct reading performance in patients overlapped completely with the previously identified semantic network, while only a minute portion of the Error > Correct map overlapped with semantic areas in the left IFG.

Inclusion of phonological impairment z-score as a covariate at the group level had no notable effect on the results. Similarly, exclusion of lesioned voxels, which constrains the analysis at each voxel to only those patients who do not have a lesion at the voxel, did not noticeably change the results.

DISCUSSION

This study shows for the first time the brain regions where neural activity is correlated specifically with successful word reading in people with aphasia. By contrasting the brain states present during correct and incorrect responses, the analysis distinguishes activation supporting successful phonologic retrieval from non-specific activation related to increased effort. Activation associated with correct word reading responses was located in the left AG. In contrast, activation associated with incorrect responses was located mainly in regions linked with attention and working memory processes (Binder, Medler, et al., 2005; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Owen, McMillan, Laird, & Bullmore, 2005), including bilateral SMA and dorsal anterior cingulate gyrus, posterior IFG and precentral gyrus, and anterior insula.

The left AG has been strongly implicated in semantic processing in healthy participants, and was the most consistently activated region in a meta-analysis of 120 functional imaging studies using semantic task contrasts (Binder et al., 2009). The left AG has also been linked with semantic processing during reading tasks in healthy controls, showing positive modulatory effects of imageability (Binder, Medler, et al., 2005; Binder, Westbury, McKiernan, Possing, & Medler, 2005; Graves, Desai, Humphries, Seidenberg, & Binder, 2010) and word frequency (Graves et al., 2010; Prabhakaran, Blumstein, Myers, Hutchison, & Britton, 2006). Word imageability (the ease with which a word evokes an associated mental image) has a weak facilitatory effect on RT in overt reading tasks (Balota, Cortese, Sergent-Marshall, Spieler, & Yap, 2004; Strain, Patterson, & Seidenberg, 1995; Woollams, 2005), suggesting that retrieving word meaning can speed computation of phonology. This idea is made explicit in the "triangle model" of word reading, in which phonologic units receive input from both orthographic and semantic representations (Plaut et al., 1996). Graves et al. (2014) showed that the degree to which healthy participants access semantic information in reading aloud, as indexed by the size of their imageability facilitation effect, is correlated with the volume of the white matter pathway connecting left AG with the posterior left superior temporal gyrus, a region implicated in phonologic retrieval (Graves, Grabowski, Mehta, & Gupta, 2008; Pillay et al., 2014). Together, these computational and empirical studies suggest that activation of semantic information can facilitate phonologic retrieval in healthy readers, and that one neurobiological mechanism for this facilitation is input from the left AG to the perisylvian phonologic system. Other ancillary support for this model comes from a performance-based study in healthy subjects examining neural activity for naming famous faces, in which activation in the left AG (Talairach coordinates -42, -56, 47; Euclidean distance from peak AG point in the present study = 6 mm) was associated with greater activation for correct compared to incorrect naming (Gesierich et al., 2012), suggesting that increased semantic access for proper nouns also boosts phonologic retrieval.

The present results are consistent with this "semantic boost" mechanism in two ways. First, the left AG was more active when correct responses were produced, suggesting that phonologic retrieval was facilitated by AG activation. Second, correctly pronounced words were, on average, higher in imageability and frequency than incorrectly pronounced words. These factors index the ease with which word meaning is retrieved (Binder, Westbury, et al., 2005; Graves et al., 2010; Monsell, Doyle, & Haggard, 1989; Paivio, 1990). Thus, the results suggest that phonologic retrieval in chronic aphasia is more likely when word meaning is successfully activated.

Although we have interpreted the left AG activation as reflecting more extensive semantic retrieval during correct trials, an alternative possibility is that this region was more extensively deactivated during incorrect trials. The concept of deactivation refers to a relative decrease in neural activity compared to a putative baseline "resting" state, however it is now widely accepted that the condition called "resting" is actually a cognitively active state involving "mind wandering", reactivation of episodic memories, future planning, and other mental activities that require complex semantic processing

(Andrews-Hanna, Saxe, & Yarkoni, 2014; Binder et al., 1999, 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Mason et al., 2007; McKiernan, D'Angelo, Kaufman, & Binder, 2006; Smallwood & Schooler, 2006; Spreng & Grady, 2010). Deactivations in fMRI studies represent, at least in part, an interruption of these ongoing conceptual processes, and it is therefore possible that purported differences in activation between stimulus conditions in the left AG instead reflect differences in deactivation, without the need to postulate differences in semantic processing of the stimuli. Given the low temporal resolution of BOLD fMRI measurements, this method cannot distinguish between deactivation followed by different degrees of activation versus different degrees of initial deactivation. We believe the latter model is unlikely for several reasons. First, the postulated mechanism underlying variation in deactivation is variation in time-on-task. That is, a longer processing time would be expected to cause longer interruption of ongoing conceptual processes, and a larger decrease in the BOLD signal after integration of the signal over time. In contrast to this prediction, we observed no areas where BOLD signal was negatively correlated with RT. This result is consistent with other fMRI studies of single word reading that found little or no negative correlation between RT and BOLD signal, even for RT variations spanning hundreds of milliseconds (Binder, Medler, et al., 2005; Binder, Westbury, et al., 2005; Graves et al., 2010). This evidence suggests that, at least on the time scale of a single-word reading task, variation in difficulty is not associated with variation in the degree of deactivation. A second weakness of the alternative model is that it offers no alternative account of why some trials lead to successful phonological retrieval. If anything, greater suppression of "default mode" activity has been reported to *improve* stimulus processing rather than the converse (Esterman, Noonan, Rosenberg, & Degutis, 2013; Smallwood & Schooler, 2006; Weissman, Roberts, Visscher, & Woldorff, 2006). Finally, the alternative model offers no account of how differences in imageability and word frequency between successful and unsuccessful trials affect brain activation or phonologic retrieval.

To our knowledge, the only previous report of enhanced brain activation during correct compared to incorrect responses in chronic aphasia was the single case studied by Meinzer et al. (2006). Correct picture naming in that case was associated with greater activation in the right IFG, with the strongest effects in the anterior IFG (pars orbitalis).

The results thus differ from the present study in linking correct response activation to an entirely different region (right IFG vs. left AG) and in the direction of the effect observed in right IFG (stronger for correct responses in Meinzer et al. vs. stronger for error responses in the present study). Several factors could account for the conflicting findings. Unlike reading aloud, picture naming necessarily requires selection of a lexical label from competing alternatives prior to phonologic retrieval. The left anterior IFG has been linked with lexical selection in a number of fMRI studies (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). Thus, right anterior IFG activation during picture naming could reflect a transfer of this selection mechanism to the right IFG in this patient. Another factor is that the current study is a composite or general result derived from a large sample of patients, thus the results capture effects that are common across individuals in the sample. It is possible that the right IFG effect observed by Meinzer et al. reflected the particular lesion pattern or premorbid language organization of their patient, and it is unknown whether this effect would be reliable across a sample. Finally, the region of right IFG implicated in the two studies is different, in that the positive effects observed by Meinzer et al. were in the anterior aspect of the gyrus, whereas the negative effects we observed were in the posterior IFG and precentral gyrus. Thus, different segments of the right IFG may have different functions in chronic aphasia recovery.

The results of our Error > Correct comparison are in general agreement with another previous performance-based fMRI study by Postman-Caucheteux and colleagues (2010), which used an overt picture naming task. Similar to our results, these authors observed activation associated with error responses in a region of the posterior right IFG in 3 patients with aphasia from left MCA stroke. Together, these results suggest that posterior right IFG activation in chronic aphasia may be a marker of effort rather than a neural correlate of successful phonologic system reorganization. Several lines of evidence provide further support for this suggestion. First, the right IFG has been implicated in working memory and cognitive control processes in many prior functional imaging studies of healthy participants (Aron, Robbins, & Poldrack, 2014; Hampshire et al., 2010; Owen et al., 2005; White et al., 2014). Second, the same posterior right IFG region associated with error responses in the present study also showed a positive correlation with time on task, suggesting sensitivity to item difficulty. This region has also shown positive correlations with RT in several prior reading studies in healthy participants (Binder, Medler, et al., 2005; Binder, Westbury, et al., 2005; Graves et al., 2010; Taylor, Rastle, & Davis, 2014). Third, suppression of the right IFG with transcranial magnetic stimulation has been shown to produce improved picture naming ability in people with chronic aphasia (Naeser et al., 2011), suggesting that activation in the right inferior frontal cortex represents maladaptive effort or maladaptive reorganization of search and selection processes when left perilesional areas are insufficient (Hillis, 2005).

In addition to the right posterior IFG, several other areas showed stronger activation during error responses, and most of these were also positively correlated with time on task. All of these regions, including the left posterior IFG, right anterior insula, bilateral precentral gyrus, bilateral SMA, and bilateral anterior cingulate gyrus, have been implicated in attention and cognitive control processes (i.e., working memory, selection, decision, error monitoring) (Owen et al., 2005), and all have shown positive correlations with RT in previous reading studies in healthy controls (Binder, Medler, et al., 2005; Binder, Westbury, et al., 2005; Graves et al., 2010; Taylor et al., 2014). Thus it is likely that during trials resulting in incorrect responses, patients were searching for and attempting to access the correct phonologic code for the target word. However, due to their phonologic system damage, they were unable to retrieve a correct or complete code, resulting in prolonged or enhanced activation of attention and search processes.

A critical feature of the present study was the selection of patients with a similar processing deficit, i.e., impaired phonology and preserved semantic access. Interactive models of language such as the triangle model predict entirely different patterns of compensation in patients with phonologic vs. semantic deficits. Initial evidence for this prediction comes from an fMRI study by Wilson et al. (2009) of 5 patients with semantic dementia. The authors observed a trend toward greater activation of the anterior parietal phonologic network when patients made regularization errors in reading irregular words (e.g., reading *sew* as "soo") than during correct responses. They proposed that the semantic impairment in their patients led to compensatory recruitment of the intact phonologic system, which is the opposite pattern from our patients with phonologic damage.

The evidence that semantic system activation can "boost" phonologic retrieval in people with phonologic system damage has important potential therapeutic implications. Specifically, this model suggests that re-training of the phonologic system might be enhanced by exercises that require explicit retrieval of word meaning along with phonology. One such therapeutic intervention that has been used to boost semantic access is called Semantic Feature Analysis (SFA). In SFA, patients are prompted with questions that provide information about distinctive semantic features associated with a target, with the goal of improving word retrieval by strengthening connections between the target and the semantic network (Rider, Wright, Marshall, & Page, 2008). SFA has been shown to improve word retrieval in patients with fluent aphasia, who generally have phonologic access impairments due to posterior perisylvian lesions (Boyle, 2004; Coelho, McHugh, & Boyle, 2000; Kiran & Thompson, 2003). Recruitment of the left inferior parietal lobule is correlated with improved behavioral outcome following SFA (Marcotte et al., 2012), and damage to the same region results in fewer treatment-related improvements in anomia compared to patients for whom this region is intact (Fridriksson, 2010). The novel finding of the current study showing reliable localization of the relevant semantic activation to the left AG provides a potential target for neural enhancement approaches such as transcranial direct current stimulation given simultaneously with such therapy.

One caveat concerning this model is that the left AG activation supporting correct responses might represent enhanced *phonologic* processing rather than enhanced semantic processing. It is possible, that is, that the damaged phonologic system has simply "expanded" into nearby AG cortex. Correct responses would then be attributed to phonologic processing in this "recruited" cortex rather than to semantic mediation. Although possible, this model provides no account of why words read correctly in the present study tend to be more imageable, a finding that clearly links the underlying activation with retrieval of word meaning.

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Figure 1.

Example trials from the behavioral tasks given for subject inclusion outside of the MRI environment. The left image shows an example of the Pseudoword Rhyme Matching task. The right image shows an example of the Semantic Picture Matching task.

Figure 2.

Lesion overlap map across 21 patients.

Figure 3.

Group z-score contrasts. (A) Correct – Error. The area active more for correctly read words (warm colors) was in the left angular gyrus. Areas active more for incorrect words (cool colors) were located bilaterally in the posterior inferior frontal cortex (mainly precentral gyrus and pars opercularis) and posterior medial frontal cortex (mainly SMA). (B) Areas modulated by RT including the bilateral SMA, posterior precuneus and lingual gyrus, and right IFG and adjacent precentral gyrus/sulcus.

Figure 4.

Overlap between performance on word reading task and semantic regions (red) in healthy controls. Activation associated with correctly read (Correct) trials is shown in green, with Semantic overlap shown in yellow. Activation associated with incorrectly read (Error) trials is shown in blue, with Semantic overlap shown in cyan.

Table 1. Patient demographic and performance data

Variable	*Mean*	*SD*	*Range*
Age	56.4	12.5	30 – 80
Education	14.7	3.2	8 – 20
Days Post Onset	1134	1491	180 – 6732
Lesion Size (ml)	73,439	58,567	6,711 – 226,978
Semantic Picture Matching	93.8	1.7	90.8 – 96.7
Pseudoword Rhyme Matching	67.5	14.1	45.8 – 87.5

Table 2.

Individual patient demographic and performance data

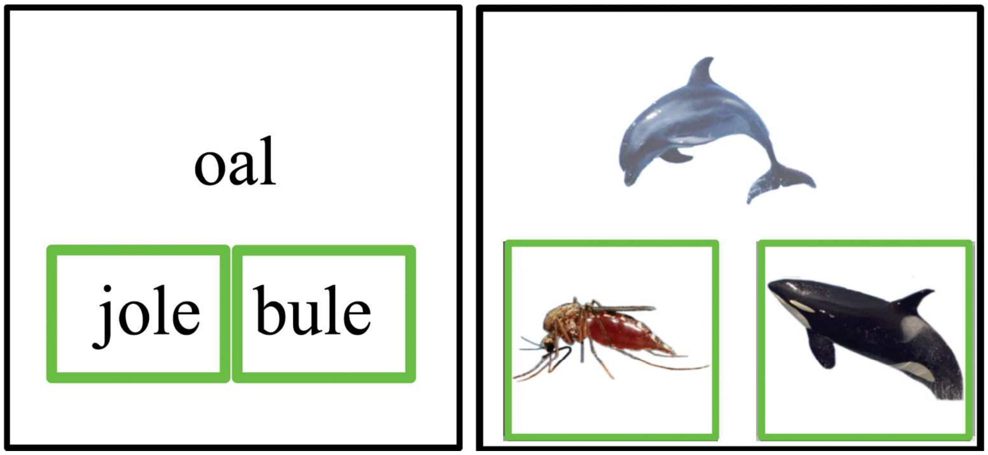
Pt.	Age	Educ.	DPO	PI	No. of lesioned voxels	Accuracy (Percent Correct) Picture Naming	Semantic Picture Matching	Pseudoword Rhyme Matching	Word Reading (fMRI)
1947	55	12	3053	-6.57	87,201	65.0	94.2	62.5	76.4
2471	80	17	658	-9.81	46,937	73.8	93.3	45.8	79.2
2477	30	14	961	-2.84	85,388	95.0	96.7	81.7	90.3
3315	49	14	255	-1.72	24,230	95.0	92.5	87.5	86.1
3326	52	20	210	-1.72	10,416	93.8	94.2	87.5	94.4
3380	61	19	726	-2.26	32,580	100.0	95.0	84.7	97.2
3383	54	14	1676	-8.46	130,491	66.3	91.7	52.8	63.9
3390	44	12	253	-1.99	72,010	93.8	95.0	86.1	97.2
3584	52	12	843	-4.14	74,148	46.3	95.0	75.0	51.4
3588	71	14	251	-6.57	23,355	27.5	92.5	62.5	27.8
3590	62	16	934	-5.49	33,329	58.8	91.7	68.1	81.9
3603	62	14	449	-6.84	71,445	80.0	91.7	61.1	69.4
3666	77	16	638	-9.54	18,597	77.5	94.2	47.2	80.6
3820	40	15	6732	-6.57	156,674	90.0	95.0	62.5	93.1
4091	57	12	2495	-1.72	68,337	98.8	95.8	87.5	95.8
4229	64	8	233	-6.03	95,698	78.8	90.8	65.3	68.1
4572	38	18	1278	-5.49	226,978	31.3	92.5	68.1	38.9
6887	55	14	1175	-7.91	184,005	28.8	95.0	55.6	45.8
8342	47	15	180	-9.27	45,489	83.8	92.5	48.6	70.8
8754	68	13	214	-7.91	48,220	61.3	92.5	55.6	91.7
9720	57	14	605	-4.69	6,711	100.0	96.7	72.2	93.1

DPO = days-post-onset, PI = phonological impairment (z-scores)

Table 3. Peak coordinates within significantly activated clusters

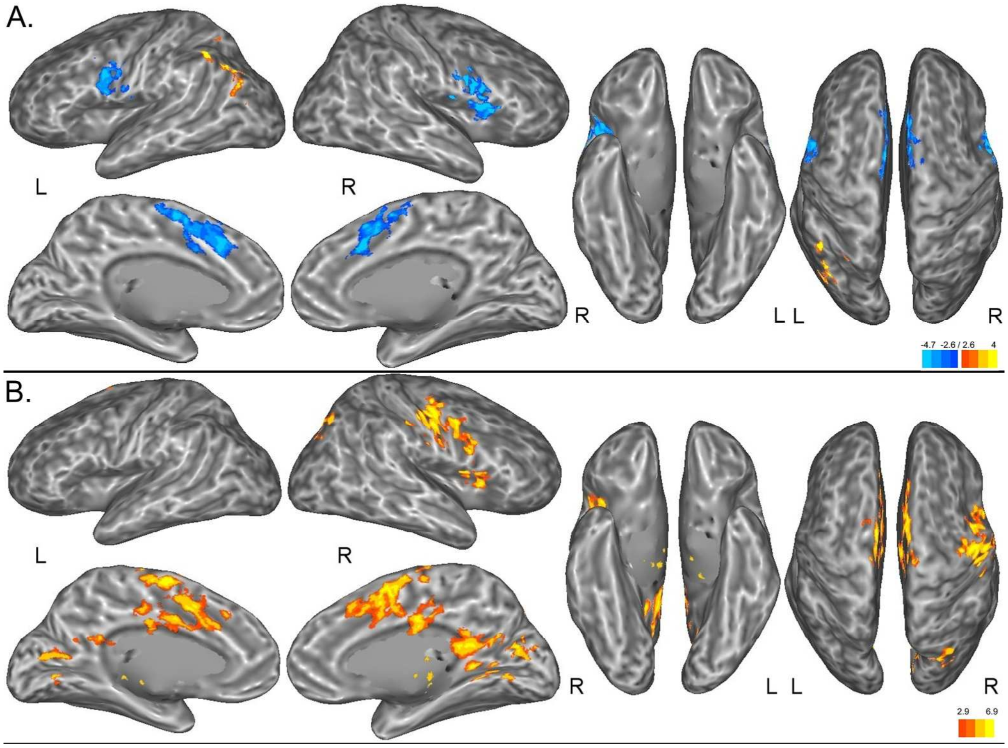
			Talairach Coordinates			
Contrast	Location of extreme point	Cluster size (µl)	X	Y	Z	Z-score
Correct	L AG	2430	-40	-52	51	3.97
Incorrect	R IFG	5388	38	8	14	-4.06
	L SMA	5833	-6	19	41	-4.74
	L IFG	3471	-36	0	24	-4.49

L = left, R = right, AG = angular gyrus, IFG = inferior frontal gyrus, SMA = supplementary motor area.



Example trials from the behavioral tasks given for subject inclusion outside of the MRI environment. The left image shows an example of the Pseudoword Rhyme Matching task. The right image shows an example of the Semantic Picture Matching task.

152x69mm (300 x 300 DPI)



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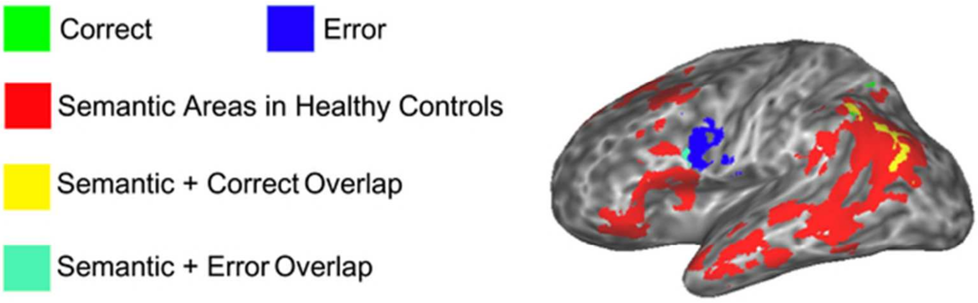
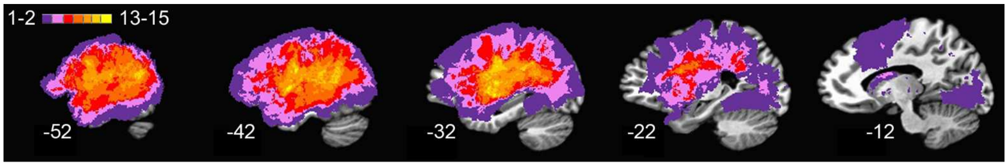
170x125mm (300 x 300 DPI)



Overlap between performance on word reading task and semantic regions (red) in healthy controls. Activation associated with correctly read (Correct) trials is shown in green, with Semantic overlap shown in yellow. Activation associated with incorrectly read (Error) trials is shown in blue, with Semantic overlap shown in cyan.

25x8mm (600 x 600 DPI)



Lesion overlap map across 21 patients.

159x25mm (300 x 300 DPI)