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Left Hemisphere Plasticity and Aphasia Recovery

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Abstract

A recent study by our group revealed a strong relationship between functional brain changes in the left hemisphere and anomia treatment outcome in chronic stroke patients (N=26) with aphasia (Fridriksson, 2010). The current research represents a continuation of this work in which we have refined our methods and added data from four more patients (for a total sample size of 30) to assess where in the left hemisphere treatment-related brain changes occur. Unlike Fridriksson (2010) which only focused on changes in correct naming as a marker of treatment outcome, the current study examined the relationship between changes in left hemisphere activity and changes in correct naming, semantic paraphasias, and phonemic paraphasias following treatment. We also expanded on the work by Fridriksson by examining whether neurophysiological measures taken at baseline (defined henceforth as the time-point before the start of anomia treatment) predict treatment outcome. Our analyses revealed that changes in activation in perilesional areas predicted treatment-related increases in correct naming in individuals with chronic aphasia. This relationship was most easily observed in the left frontal lobe. Decrease in the number of semantic and phonemic paraphasias was predicted by activation change in the temporal lobe involving cortical areas that were shown to be active during picture naming in 14 normal subjects. In contrast, a far less certain relationship was found between baseline neurophysiological measures and anomia treatment outcome. Our findings suggest that improved naming associated with behavioral anomia treatment in aphasia is associated with modulation of the left frontal lobe whereas reduction in naming errors is mediated by left posterior regions that classically are thought to be involved in language processing.

Keywords

aphasia; anomia; MRI; language; speech

1. Introduction

Recovery from aphasia following stroke varies considerably. In most individuals, some spontaneous recovery occurs in the early phases of stroke with the greatest return in function seen in the first few weeks following stroke onset (Maas et al., in press; Pedersen et al.,

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1995). The extent of spontaneous recovery is associated with stroke severity and related factors such as lesion size and location (Plowman et al., in press). It is likely that similar stroke factors, such as sparing and recruitment of specific brain regions, may also relate to the success of aphasia treatment.

Debates have persisted for over a century concerning the manner in which the brain compensates in the recovery process (e.g., Calvert et al., 2000; Cao et al., 1999; Heiss & Thiel, 2006; Hillis, 2006; Hillis & Heidler, 2002; Meinzer & Breitenstein, 2008; Pulvermuller et al., 2005; Saur et al., 2006; Thompson, 2000; Weiller et al., 1995). Traditionally, the right hemisphere is thought to support recovery: for example, left hemisphere stroke patients with accompanying aphasia experience further deterioration in language abilities following right hemisphere stroke or sodium amytal injection targeting the right hemisphere (Berthier et al., 1991; Kinsbourne, 1971; Levine & Mohr, 1979). In a more recent study of a single patient, Turkeltaub and colleagues (in press) demonstrated how transcranial magnetic stimulation aimed at depressing activation of the right *pars triangularis* resulted in increased naming in a patient with non-fluent aphasia. Following a subsequent stroke involving the right hemisphere, the patient experienced relatively increased language impairment leading the authors to suggest that distinct regions of the right hemisphere may play different roles in aphasia recovery. Although it is possible that right hemisphere regions may assume language functioning that supports recovery from aphasia, several studies have also revealed aphasic language recovery associated with left hemisphere recruitment (e.g., Cornelissen et al., 2003; Crinion & Leff, 2007; Fridriksson, 2010; Postman-Caucheteaux et al., 2010).

During the past decade, a number of small group and single case studies have examined functional brain changes associated with aphasia treatment outcome (e.g., Breier et al., 2007; Crosson et al., 2005; Davis, Harrington, & Baynes, 2006; Fernandez et al., 2004; Leger et al., 2002; Martin et al., 2009; Peck et al., 2004; Postman-Caucheteaux et al., 2010; Pulvermuller et al., 2005; Rosen et al., 2000; Vitali et al., 2007; Wierenga et al., 2006). Not surprisingly, results have varied widely with regard to where in the brain favorable changes were revealed. Very limited evidence relates the extent of treatment success to the magnitude of functional brain changes. For example, in one of our earlier studies (Fridriksson et al., 2006a), three individuals with chronic aphasia underwent three functional MRI (fMRI) sessions before and after 40 hours of aphasia treatment. As is common in such research, they varied considerably with regard to clinical profile and lesion characteristics. Functional brain changes associated with the treatment also varied extensively among the patients. Although emphasizing that change in functional brain activity is somehow related to change in language task performance, this study and other similar ones contribute only minimally to our overall understanding of where brain changes related to aphasia recovery occur. That is, such studies seem more likely to emphasize individual patient differences rather than similarities.

A potentially more fruitful approach to this problem is to treat a relatively large number of patients using a single treatment protocol and then relate treatment outcome to functional brain changes in a systematic way. For example, we recently administered the same anomia treatment protocol (a linguistic cueing hierarchy) to individuals (N=26) with chronic stroke and various types and severities of aphasia (Fridriksson, 2010). Response to treatment varied widely among the patients in that at least half showed no benefit or very limited benefit from treatment while ten patients experienced a relatively robust response. Interestingly, treatment outcome was not associated with aphasia severity or type; out of the individuals who benefited most from the treatment, six had fluent aphasia while the remaining four had non-fluent aphasia. Treatment success was related to location and extent of functional brain changes. Those who responded well showed a corresponding increase in left hemisphere

activity – no similar changes occurred in the poor responders. Moreover, damage to certain posterior left hemisphere regions was a negative predictor of treatment success. Individuals whose brain damage involved posterior-inferior portions of the left temporal lobe and, to a lesser extent, the medial occipital lobe, were less likely to benefit from treatment compared to patients in whom those regions were largely spared. Based on these data, it seems reasonable to suggest that anomia treatment utilizing a cueing hierarchy approach is probably not warranted in patients with damage to the left posterior temporal lobe and adjacent regions. Similarly, it appears that anomia treatment success, at least when utilizing a hierarchy of linguistic cues, is strongly related to left hemisphere recruitment.

Although considerable evidence suggests left hemisphere plasticity supports treated anomia recovery, less is known about the specific cortical patterns of this reorganization. Animal models of acute stroke suggest that brain plasticity is enhanced in perilesional areas (defined here as cortex immediately adjacent to the frank lesion) where neural sprouting is enhanced (Nudo, 1999; Stroemer et al., 1995). Thus, it seems plausible that functional brain changes underlying aphasia recovery rely on the perilesional cortex. Similar findings have been found in single case or small group studies (e.g., Fernandez et al., 2004; Fridriksson et al., 2006a; Martin et al., 2009; Rosen et al., 2000; Wierenga et al., 2006). However, treated aphasia recovery could also possibly rely on the residual left hemisphere language network. That is, intact brain regions that premorbidly supported language processing may now also, in addition, assume some of the role previously played by language regions that were directly affected by the stroke. Whereas reorganization that primarily relies on the residual language network seems feasible, our previous study (Fridriksson, 2010) suggested that a proportion of the functional brain changes that correlated with treated anomia recovery occurred in regions that classically would not be considered primary language cortex (e.g., left superior parietal cortex and precuneus). However, cortical damage that results in aphasia must (at least indirectly) affect the cortical language areas, although some of the language network may still be structurally intact. Therefore, it is possible that improvement in anomia recruits most heavily those residual language regions that are adjacent to the actual lesion (i.e., areas that are both residual and perilesional).

To date, much of the discussion regarding plasticity associated with aphasia recovery has centered on cortical location. Although understanding where favorable cortical changes associated with aphasia recovery occur in the brain has both theoretical and practical implications (e.g., for targeting brain stimulation treatments), very little effort has focused on the reasons why these changes occur in certain regions rather than somewhere else in the brain. In a recent study, Richardson et al. (2011) found that cerebral perfusion in chronic stroke is significantly reduced in perilesional regions as well as in the remainder of the ipsilesional hemisphere in comparison to the spared hemisphere. A few studies have demonstrated impaired blood oxygenated level dependent (BOLD) signal in areas of impaired cerebral perfusion (Bonakdarpour et al., 2007; Fridriksson et al., 2006b; Thompson et al., 2010). If decreased cerebral perfusion is common in chronic stroke, then changes that favorably mediate recovery may relate to the extent of cerebral perfusion in areas that are crucial for treatment outcome. It seems possible that the state of brain tissue that appears intact on structural MRI may predict aphasia treatment outcome and, consequently, the extent of functional brain changes. Beyond lesion size and location, we know almost nothing about how other factors such as cerebral perfusion may influence aphasia treatment success and location of concomitant brain plasticity. If, indeed, anomia recovery mediated by language treatment relies on functional brain changes (as measured by fMRI) in the left hemisphere, it would seem that such changes would relate to the baseline physiology (i.e., physiological measures taken before initiation of anomia treatment) of the left hemisphere. Moreover, it is likely that the neurophysiology of the stroke-affected brain may influence the extent and location of functional brain changes associated with aphasia treatment.

The current research represents a continuation of Fridriksson (2010) where treatment-related improvement in correct naming was found to be associated with increased left hemisphere activity in patients with chronic aphasia. Specifically, our aim was to better characterize these left hemisphere changes in a larger sample of patients. Accordingly, the purpose of this research was twofold: 1. To compare the role of perilesional cortex to that of the residual language network in the left hemisphere as the locus of favorable brain changes that support treated anomia recovery in patients with chronic stroke-induced aphasia. As these changes may overlap in some patients, we also examined perilesional cortex within the residual language network as a predictor of anomia treatment success. 2. To increase our understanding of how cerebral blood flow and brain activation assessed prior to treatment initiation relate to improved ability to name pictures following treatment.

2. Materials and Methods

2.1 Patients

Each of the 30 patients (16 females; age range = 33–81 years; $M = 59.2$ years) included in this study incurred a single stroke (ischemic and/or hemorrhagic) in the left hemisphere at least 6 months prior to participation ($M = 51.1$ months, range = 6–350 months). All were evaluated with the Western Aphasia Battery (WAB; Kertesz, 1982). Based on their test scores, each obtained an aphasia quotient (AQ), a measure of aphasia severity ranging from 0 to 100 (>93.8 indicates language abilities within normal limits). The mean AQ for the group was 57.94 ($SD=25.8$) with the following aphasia subtypes represented: 13 Broca's, 10 anomic, 3 conduction, 2 Wernicke's, 1 trans-cortical motor (TCM), and 1 global. Patient data are reported in Table 1 and a lesion overlay map representing damage in all 30 patients is shown in Figure 1. Data from 26 of these 30 patients were also reported in Fridriksson (2010). The study was approved by the University of South Carolina's Institutional Review Board, and all provided informed consent.

2.2 Treatment

Patients received three hours of anomia treatment per weekday for two weeks, for a total of 30 hours. The treatment targeted oral naming of concrete, imageable nouns and relied on a cueing hierarchy involving five levels of phonological or semantic cues administered in an ascending order of cueing strength. Half of the patients received treatment using the phonological cueing hierarchy during the first week and, after a week rest period, received treatment for a week using the semantic cueing hierarchy; the order of treatment was reversed for the remaining half of patients. Each cueing hierarchy targeted a separate corpus of 80 mid- to high-frequency nouns (Kucera & Frances, 1967). Treatment outcome was defined as the treatment-related change in correct naming attempts, semantic paraphasias, and phonemic paraphasias. Naming improvement was assessed by comparing overt naming performance during the two pre-treatment and two post-treatment fMRI sessions where participants attempted to name pictures targeted in treatment. Specifically, change in naming was quantified by subtracting the number of specific naming attempts (correct naming, semantic paraphasias, and phonemic paraphasias) during two pre-treatment naming sessions from the naming attempts in two post-treatment naming sessions.

2.3 Neuroimaging

MRI scanning relied on a 3T Siemens Trio system equipped with a 12-element head-coil. For one patient MRI at 3T was contraindicated. Thus, twenty-nine patients were scanned with high-resolution (1mm^3 voxels; 160 sagittal slices) T2 and T1 MRI as well as fMRI sequences described previously (e.g., Fridriksson, 2010). Structural images were prepared for data analyses using software designed and supported by the Oxford Centre for Functional MRI of the Brain (FMRIB) – FMRIB's Software Library (FSL) version 4.1

(Smith et al., 2004). Lesions and cost-function masks were demarcated on axial slices of native T2-MRI images using MRICron (<http://www.cabiatl.com/mricro/mricron/index.html>). Cropped and skull-stripped structural MRI images were normalized to the standard MNI 152 template, employing cost-function mask weighting for improved accuracy. The transformation matrix for normalization was applied to the lesion. Normalized images were resliced to 2 mm isotropic.

2.3.1 fMRI—During fMRI scanning, patients participated in the overt naming task described previously (Fridriksson, 2010; Fridriksson et al., 2006, 2007, 2009, 2010). Briefly, patients viewed 120 randomly presented pictures, 80 of which depicted real objects for overt naming and 40 of which were abstract pictures requiring no response. During this naming task, 2 s (TA=2s) sparse acquisition of whole brain supratentorial volumes occurred every 10 s (TR=10s). Pictures were presented during the 8 s silent period between volume acquisitions and the timings of inter-stimulus-intervals were jittered to improve modeling of the hemodynamic response. Pictured stimuli were back-projected onto a screen situated at the end of the scanner bore and viewed via a mirror mounted on the head coil. All naming attempts were recorded using a non-ferrous microphone and digitally stored for offline scoring by a speech-language pathologist with extensive experience treating aphasia.

All fMRI data were analyzed using FSL (FMRIB's Software Library) version 4.1 (Smith et al., 2004). To appreciate how treatment-induced changes in naming ability relate to modulation of left hemisphere activity, the fMRI data were subjected to a three-level analysis: 1. T2* fMRI data collected during each of four scanning sessions (two pre- and two post-treatment sessions) were analyzed using the following pre-processing parameters: high-pass filter cutoff = 100 s; motion correction using linear image registration (Jenkinson et al., 2002); and spatial smoothing (FWHM) = 6 mm. A time-series statistical analysis involving all stimulus presentations, regardless of response, relied on general linear modeling with local autocorrelation correction (Woolrich et al., 2001). The time series data were normalized to each patient's T2-MRI in standard space using linear transformation and 12 degrees of freedom. The second level analysis contrasted the two fMRI sessions before treatment with the two fMRI sessions administered upon treatment completion, creating a single statistical map for each patient that represented the change in cortical activation from pre-treatment to post-treatment. The final level included summarizing baseline levels of cortical activation (i.e., naming-related cortical activation assessed in the two fMRI sessions administered before treatment was started) as well as change in activity in three patient specific volumes of interest (VOIs). Further detail on selection of the VOIs is described below under 'Mask Creation for Selected Cortical Areas.'

2.3.2 Pulsed arterial spin labeling (PASL)—Two PASL sequences were used to acquire regional cerebral blood flow (rCBF) measures in this study. Twenty-one patients were scanned with the following parameters: parallel imaging GRAPPA factor = 2, $3.5 \times 3.5 \times 6$ mm voxels, 16 axial slices, TR = 4000 ms, TE = 12 ms. Five were scanned with the following parameters: parallel imaging GRAPPA factor = 2, $3 \times 3 \times 6$ mm voxels, 14 axial slices, TR = 2500 ms, TE = 11 ms. Images were corrected for head motion. Each patient's perfusion image was coregistered to his or her own spatially normalized structural T1 image. Note that of the 30 patients included in this study, 26 underwent PASL.

2.4 Mask Creation for Selected Cortical Areas

Based on aforementioned evidence suggesting the importance of perilesional areas in aphasia recovery, we sought to compare various measures in the perilesional cortex to areas commonly associated with language processing. Thus, we developed perilesional and residual masks (as defined below) for each participant that reflected their unique pattern of

damage, and which could be overlaid on different image types allowing us to obtain values for functional activation (fMRI) and cerebral perfusion (CBF). As there was considerable overlap between the perilesional and residual areas, masks were divided into three primary volumes of interest (VOIs): 1. Perilesional cortex that excluded residual naming areas; 2. Residual naming areas that excluded perilesional cortex; and 3. Overlapping perilesional and residual naming areas. These VOIs were each subdivided into the three lobes (frontal, parietal, temporal) typically implicated in language processing, to allow comparison across these regions; lobes were defined using lobe masks derived from the Wake Forest Pickatlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003). Thus each subject had a total of nine masks – three VOIs, each subdivided into three lobes. Mask creation, as well as data extraction, was performed using MATLAB 2010b (Mathworks, Inc.).

2.4.1 Perilesional mask creation—There is no current evidence defining the spatial parameters of what might be coined the ‘perilesional area.’ Therefore, we addressed this issue here. Because cerebral perfusion deficits correlate both with reduced functional activation and behavioral deficits in acute and chronic stages of stroke recovery (Hillis et al., 2005, 2006; Love et al., 2002; Thompson et al., 2010), we used CBF values to guide our decision regarding how far perilesional masks should extend, as reduced values might represent those cortical areas around the lesion that need to be “recruited” after stroke for optimal behavioral outcomes. Previous research suggested that patients with chronic stroke, as a group, demonstrate significantly lower perfusion in the perilesional region extending at least 8 mm beyond the lesion than in both the remaining intact hemisphere and the contralateral hemisphere (Richardson et al., 2011). However, since the ipsilesional intact cortex also demonstrated CBF values that were significantly lower in comparison to the contralateral hemisphere, we sought to determine how far reduced CBF values extend beyond the frank lesion, and, based thereon, determine the size of the perilesional VOIs used in the current analyses.

To determine the size of the perilesional cortex, CBF was assessed as a function of distance from the actual lesion in a subset of 20 patients (12 females; age range = 41 to 81 years; $M = 61.3$) using MRIcron. Lesions were dilated into seven adjacent 3 mm perilesional regions expanding 24 mm beyond the lesion’s rim (i.e., 3–6 mm, 6–9 mm, 9–12 mm, etc.). The region 0 to 3 mm beyond the lesion’s rim was excluded to account for partial volume effects (as in Richardson et al., 2011). The seven perilesional regions were masked using a probabilistic left hemisphere gray matter mask so that CBF values were only obtained from gray matter. The resultant perilesional gray matter masks were overlaid onto each patient’s standardized CBF image. Mean CBF for each mask was obtained in units of mL/min/100g of tissue.

Planned comparisons between successively more distant perilesional masks were conducted to examine the differences in CBF values, in an attempt to determine the extent of how far reduced CBF might extend beyond frank cortical damage. When comparing the adjacent regions to one another, the analysis produced significant differences (Bonferroni corrected for 6 comparisons) between the following: 1) 3–6 mm and 6–9 mm ($p = .0001$), 2) 6–9 mm and 9–12 mm ($p = .0003$), and 3) 9–12 mm and 12–15 mm ($p = .004$), suggesting that significantly reduced CBF extends as far as 12–15 mm beyond the lesion. Significant differences between masks more distant from the lesion were not observed. Based upon these group results where hypoperfusion extended as far as 12–15 mm beyond the lesion, perilesional masks extending from 3–15 mm beyond the lesion’s rim were created on a patient-by-patient basis and are defined as the ‘perilesional cortex’ in the frontal, parietal, and temporal lobes (Figure 2A).

2.4.2 Residual mask creation—To determine the size and location of residual naming-related cortical areas among the current sample of patients with aphasia, fourteen healthy, right-handed subjects (age range = 26 to 77 years) with normal speech-language abilities participated in the same fMRI naming task used with the aphasic patients. The fMRI data analysis relied on default setup in FSL including the following parameters for preprocessing: motion correction, spatial smoothing using Gaussian kernel of FWHM 8.0mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high-pass temporal filtering (sigma=60.0s). All functional images were normalized before being entered into a group analysis. Z statistics images for the contrast ‘naming>watching abstract pictures’ were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = .05$. Then, a group mean activation map of the network associated with naming was defined, as shown in Figure 2B. To maintain consistency with perilesional mask creation, the frank lesion and the surrounding 3 mm were deleted from the mask for each subject. The resulting map was divided according to its distribution within the frontal, parietal, and temporal lobes; these images formed each subject’s residual network masks.

2.4.3 Volumes of interest—To create each subject’s final VOIs, the residual masks were overlaid onto the perilesional masks, so as to subdivide the perilesional areas which were within the residual naming network (perilesional-residual overlap) from those that were not (perilesional only); this also yielded masks which were specific to the residual network (residual only). The residual activation maps were then thresholded separately within each lobe, so that the average number of voxels in the residual only masks matched the average number of voxels in the perilesional only masks allowing for direct comparison between these areas. Z-score thresholds and average number of voxels (SD) for each volume of interest were as follows – frontal: $z = 2.366$, residual only voxels = 5402.1(3273.0), overlap = 2604.7(1397.8), perilesional only = 5405.6(3272.9); parietal: $z = 1.874$, residual only voxels = 2087.8(1609.6), overlap = 1542.5(755.5), perilesional only = 2085.1(965.5); temporal: $z = 1.427$, residual only voxels = 2435.3(2517.0), overlap = 2636.4(1154.6), perilesional only = 2436.0(1348.0). Figure 2C illustrates the three different VOIs (overlap, perilesional only, and residual only) in a single patient.

2.5 Data Analyses

2.5.1 Independent factors—Summary measures were determined in each of the VOIs within each lobe, for each of the three data sets (baseline fMRI activation, change in fMRI activation, and CBF). Because our masks often included areas of large spatial extent, we used the average value of the top ten percent of voxels from each mask as the summary measure for fMRI data. This constrained the analyses to the most robust data points. Visual inspection of the frequency histograms for CBF data yielded slight positive skew; accordingly, the median was used as the summary measure.

2.5.2 Dependent factors—To assess overall change in naming, three dependent factors defined “change”: 1. Correct naming (ACC); 2. Semantic paraphasias (SEM); and 3. Phonemic paraphasias (PHON). As stated earlier, the change in correct naming and paraphasias was determined by subtracting the number of correct naming attempts, semantic paraphasias, and phonemic paraphasias before the start of the anomia treatment phase from the same kinds of naming attempts once treatment was completed.

2.5.3 Statistical analyses—Statistical analyses were completed using SPSS 19.0.0 (SPSS, Inc.). For aim one, to evaluate the brain regions in which activation change is most predictive of how one responds in treatment, multiple linear regression analyses were performed. First, for the three VOIs (overlap, perilesional only, residual only), data from

each of three left hemisphere lobes (frontal, parietal, and temporal lobes) were entered into the analysis, with missing cases excluded in a pairwise fashion. The explanatory power of the resulting regression model was determined by the R^2 (proportional reduction in error). Then, to determine if certain cortical areas were relatively stronger predictors of outcomes, factors of interest were entered into a regression analysis using a stepwise approach. For the second aim, to evaluate baseline neurophysiological factors as predictors of treatment response, the same regression analyses described for aim one were employed – one for each data type (baseline fMRI and CBF) separately, again beginning with the full model, followed by stepwise regression.

3. Results

Thirty patients completed all behavioral testing and 30 hours of anomia treatment. A comparison of pre- and post-treatment naming performance across the whole group revealed a statistically significant increase in correct naming, $t(29)=4.76$, $p<.001$, and a decrease in semantic paraphasias, $t(29)=3.79$, $p<.001$, but not in phonemic paraphasias, $t(29)=.23$, $p=.82$. Although not a direct goal of this research, the influence of age, time post-stroke, aphasia severity, and aphasia type upon treatment outcome was explored. Neither age or time post-stroke (tp-s) were associated with change in correct naming (age: $r=-.25$, $p=.18$; tp-s: $r=.04$, $p=.85$), semantic paraphasias (age: $r=-.28$, $p=.14$; tp-s: $r=.01$, $p=.99$), or phonemic paraphasias (age: $r=.02$, $p=.94$; tp-s: $r=-.14$, $p=.46$). Similarly, no relationship was found between overall aphasia severity (measured as AQ) and change in correct naming ($r=-.27$, $p=.18$), semantic paraphasias ($r=.22$, $p=.26$), or phonemic paraphasias ($r=-.13$, $p=.49$). To better understand if aphasia type was related to treatment outcome, a regression analysis including a categorical predictor (aphasia type) was performed with change in specific naming attempts as the dependent factor. This analysis revealed that aphasia type (summarized in three categories: 1. Anomic aphasia; 2. Broca's, TCM, and global aphasia; and 3. Wernicke's and conduction aphasia) was not related to change in correct naming, $F(2,27)=1.11$, $p=.34$, or phonemic paraphasias, $F(2,27)=1.11$, $p=.34$. However, change in semantic paraphasias was related to aphasia type, $F(2,27)=9.9$, $p<.001$. Patients with Broca's, TCM, or global aphasia experienced a smaller reduction in semantic errors than those with anomic aphasia ($p=.001$). Although a similar analysis did not reveal less reduction in semantic paraphasias in patients with Broca's, TCM, or global aphasia compared to those with Wernicke's or conduction aphasia, a trend towards a statistically significant difference was found ($p=.054$).

3.1 Brain Changes Associated with Treatment Outcome

To examine the relationship between treatment-related increase in correct naming and change in left hemisphere activity, we calculated three linear regression analyses separated according to VOI – overlap, perilesional only, and residual only. Then, the strength of the relationship between increase in correct naming and activation change (in frontal, parietal, and temporal lobes) was compared among the three VOIs based on proportional reduction in error (R^2). The strongest predictor of increase in correct naming was found for in perilesional cortex, $R^2=.30$, $p=.035$ (Table 2). More specifically, step-wise regression revealed that the perilesional frontal lobe was the most robust predictor of correct naming improvement, most strongly in the residual naming areas, $F(1,25)=5.27$, $p=.03$ (Figure 3A), but also in perilesional areas not previously recruited for naming, $F(1,26)=5.08$, $p=.033$. To examine whether the above results reflected overall change in naming attempts, rather than actual improvement in correct naming, the regression analyses were run utilizing the same independent factors but with total change in naming responses, regardless of accuracy, as the dependent factor; no significant results were revealed.

The regression analyses described above were also calculated including treatment-related change in phonemic and semantic paraphasias as dependent factors. Change in semantic paraphasias, $R^2=.30$, $p=.038$, and phonemic paraphasias, $R^2=.50$, $p=.001$, was predicted by activation change occurring in the residual language network (Table 2). More specifically, a step-wise regression analysis revealed change in semantic paraphasias was most robustly predicted by activation change in residual naming areas in the temporal lobe, $F(1,25)=9.57$, $p=.005$ (Figure 3B). A similar analysis revealed that change in phonemic paraphasias was predicted by activation change involving residual naming areas in the temporal and parietal lobes, $F(1,25)=11.89$, $p=.0001$ (Table 2; Figure 3C). As can be seen in Figure 3B and 3C, one patient with Broca's aphasia experienced considerably greater increase in temporal lobe activation compared to the rest of the group. To determine the influence of this single patient on the overall results for naming errors, his data were removed and the analyses were repeated. Without this data point included, change in semantic errors was not predicted by overall change in activation in the residual language areas, $R^2=.21$, $p=.15$. However, a step-wise regression revealed that activation change in temporal lobe regions involved in picture naming in normal participants was related to change in semantic errors, $F(1,24)=5.28$, $p=.031$. The analyses were also repeated for change in phonemic paraphasias. Overall, the same results prevailed as when the patient's data were included: Change in phonemic paraphasias was predicted by overall activation change in residual naming areas, $R^2=.48$, $p=.002$. More specifically, a step-wise regression revealed that activation change in residual naming areas involving the temporal and parietal lobes predicted change in phonemic paraphasias, $F(1,24)=10.14$, $p=.001$.

3.2 Ipsilesional Neurophysiology Associated with Treatment Outcome

To examine whether baseline physiology (CBF and pre-treatment activation associated with picture naming) related to anomia treatment outcome, linear regression analyses were implemented using the VOIs described in the previous section. That is, levels of CBF and baseline cortical activation in the three VOIs were used to predict treatment-related change in correct naming, semantic paraphasias, and phonemic paraphasias; see Table 2 for results. Increase in correct naming was predicted by CBF values in the residual language network, $R^2=.36$, $p=.022$. Change in semantic paraphasias was predicted by baseline activation in overlapping areas, $R^2=.38$, $p=.01$. More specifically, step-wise regression analyses revealed that change in semantic paraphasias was predicted by baseline activation in perilesional areas in the frontal lobe, $F(1,26)=7.37$, $p=.012$.

4. Discussion

The current work represents an extension of our previous study that showed that left hemisphere increase in brain activation is associated with treatment-related increase in correct naming among patients with chronic aphasia (Fridriksson, 2010). Whereas that study used a univariate analysis to appreciate the relationship between treatment-related change in correct naming and brain activation, the current study applied a multivariate approach. Based on work showing enhanced neural sprouting in the perilesional cortex following brain damage (Nudo, 1999; Stroemer et al., 1995), our aim was to target the regions immediately surrounding frank damage in the left hemisphere. However, visual inspection of the data suggested that damage to the residual naming network (qualified as naming-related brain activation in 14 normal participants) varied substantially among the patients studied. Therefore, we refined our search within the left hemisphere to include what happens in brain regions typically activated during picture naming outside the perilesional cortex (residual naming network only) as well as naming-related areas within the perilesional network (overlap between perilesional areas and naming-related areas). Finally, aforementioned

perilesional cortex that did not include residual naming areas (perilesional regions, only) was examined.

Overall activation increase in left hemisphere perilesional areas was found to be a significant predictor of treatment-related improvement in correct naming; this relationship was strongest in the frontal lobe. As is evident in Figure 3A, slightly fewer than half of the patients demonstrated little or no improvement in naming whereas the remaining patients were able to name at least 10 more pictures (out of 80 total) than they were able to name at baseline following treatment completion. This improvement was not related to aphasia type or severity. Therefore, we conclude that treatment-related increase in brain activation among regions surrounding frank cortical damage supports improved naming accuracy, regardless of aphasia type. One account for increased left frontal activity associated with increase in correct naming might suggest that participants were simply naming more items, regardless of accuracy, after treatment was complete. However, no relationship was found between changes in cortical activity and overall increase in naming attempts. This finding would suggest that a pure motor-speech explanation could not account for the data. In a recent meta-analysis involving the anatomy of language in 100 studies (Price, 2010), activation in the left middle-frontal gyrus was found to be associated with lexical retrieval. Although several competing hypotheses could be proposed to explain our findings, we suggest that greater reliance on the left frontal lobe could reflect treatment-related improvements in lexical retrieval.

Change in the number of naming errors, both semantic and phonological, was primarily driven by temporal lobe regions that, prior to the stroke, were involved in picture naming. Unlike what was seen for treatment-related change in correct naming, where greater accuracy was associated with increased activity, reduction in semantic and phonological errors was negatively associated with increases in temporal lobe activation, such that a relatively smaller increase in activation was related to a decrease in naming errors. In the case of phonological errors, the same was true for residual naming areas in the parietal lobe. Based thereon, anomia treatment that promotes increase in correctly named items would be associated with increased frontal activity whereas reduction in naming errors would be expected to be reflected in relatively less activation change in posterior regions. This relationship was particularly salient in regard to phonemic paraphasias, where 50% of the variance for error reduction was explained by activation changes in residual naming areas in the temporal and parietal lobes. Notably, the areas implicated here are roughly the same as those classically associated with normal language processing (e.g., Binder et al., 1997; Hickok & Poeppel, 2007). Therefore, it is perhaps not surprising that changes in semantic errors are reflected by activation changes in cortical areas that were crucial for semantic processing before the initial stroke (i.e., the left temporal lobe). In regard to changes in phonemic paraphasias, a similar account could be proposed. That is, phonological processing in normal participants is commonly found to tax both temporal and parietal regions (e.g., Binder et al., 1997, 2000; Buchsbaum, Hickok, & Humphries, 2001; Démonet et al., 1996; Hickok & Poeppel, 2007); accordingly, it seems plausible that reductions in phonemic paraphasias would be reflected in functional reorganization among areas that are recruited for phonological processing in normal subjects.

Although increases in correct naming are typically reported as an indicator of treatment-related anomia recovery, it is clear that reduction in naming errors would also have to be considered a marker of improved naming accuracy for most patients with aphasia. Taken together, it appears that increased activity in specific left hemisphere regions (primarily in the residual naming areas) may be important for anomia treatment success. However, the extent of recovery, qualified as increases in correct naming or decreases in errors, may rely on dynamic activation changes that vary by cortical region. For example, too much increase

in temporal lobe activation may signify greater phonological or semantic impairment, at least as assessed with overt naming, while more moderate increase in activation may be more favorable for anomia treatment outcome. In contrast, greater activation in perilesional frontal lobe regions suggested improvements in correct naming whereas those patients with relatively less increase in activation showed less favorable treatment outcome.

Although we believe that the multivariate approach used in the current study constitutes a significant methodological improvement over Fridriksson (2010), it is likely that a network analysis involving successful multi-modal integration of MRI data (e.g. fMRI and ASL) would better capture brain changes that drive aphasia recovery. Only a few studies have utilized network analyses of functional or structural connectivity (Carter et al., 2010; Crofts et al., 2011; Solodkin et al., 2004), or a combination of the two (Specht et al., 2009), in patients with stroke. No group studies have yet comprehensively integrated such data in a prospective study of aphasia recovery. Whereas the current study is believed to be the first to comprehensively reveal a relationship between specific left hemisphere regions and treated anomia improvement in chronic stroke, further methodological improvements in future studies that emphasize cortical connectivity (both structural and functional), as well as integration of data from multiple modalities, are key for better understanding of neurophysiological changes underlying aphasia recovery.

Our findings suggest that the left hemisphere supports treated anomia recovery in aphasia (Fridriksson, 2010). More specifically, this work suggests that such recovery is mediated by specific left hemisphere regions either involving the perilesional cortex or cortical regions activated by picture naming in normal participants. However, the relationship between CBF and the BOLD signal measured at baseline and the success of anomia treatment was far less clear. Even though a couple of regression analyses yielded statistically significant results, a general pattern indicating that the level of baseline cortical activation (during picture naming) or CBF, and anomia treatment outcome did not emerge. Although baseline fMRI has been shown to predict recovery in aphasia (e.g., Richter et al., 2008), our results do not provide strong corroborating evidence, as baseline brain activation predicted only the change in semantic errors. Indeed, from these results, it seems that measuring language-related activation in specific left hemisphere regions before treatment initiation might be of limited clinical importance. Regarding perfusion, we recently reported that CBF is decreased in the perilesional cortex in chronic stroke (Richardson et al., 2011). The current study did not show the level of CBF in perilesional cortex to be associated with anomia treatment success in chronic stroke. However, CBF level in residual naming areas was a significant predictor of change in correct naming, perhaps providing some evidence that cerebral perfusion in chronic stroke might be related to treatment potential. Whereas ASL provides an absolute measure of CBF (Lee et al., 2006) and has been cross-validated with H₂O₁₅ positron emission tomography (PET; Chen et al., 2011, Ye et al., 2000), it is primarily used for research applications (Alexopoulos et al. 2011, Lim et al., 2010, Pimentel et al., 2011) and has not undergone rigorous testing for clinical applications; the results presented here should be interpreted accordingly. It is also worth noting that a handful of studies have examined the relationship between abnormal hemodynamics and the BOLD signal in stroke. For example, a case study by Fridriksson et al. (2006b) revealed slower than normal cerebral perfusion in specific cortical regions in a patient with chronic stroke and that this slowing was related to an abnormal BOLD signal. Utilizing data from six patients with chronic stroke, Thompson and colleagues (2010) looked specifically at the relationship between time-to-peak (TTP) of the BOLD signal and CBF measured with arterial spin labeling and found that slower TTP had a modest correlation with lower CBF. Based thereon, further studies that relate measures of cerebral hemodynamics to brain activation in larger samples of stroke seem necessary to determine the specific nature of this relationship.

In an attempt to define the boundaries of what we have referred to here as ‘perilesional’ cortex, we examined the level of CBF as a function of distance (in 3 mm spatial increments) from the actual lesion in a subset of patients enrolled in this study. A gradual increase in CBF was found for areas extending to 15 mm from the lesion boundary and we defined this boundary as the edge of the perilesional cortex. Other physiological measures may emerge in future studies to better qualify what constitutes perilesional cortex. In the absence of available evidence defining the boundaries of perilesional cortex, we felt that our method was the most principled way to define this region. We are unaware of other studies that used this approach to scrutinize potential CBF changes surrounding damage in chronic stroke.

5. Conclusions

In summary, our findings suggest that functional brain changes in physiologically defined perilesional cortex, especially in the frontal lobe, predict improvement in correct naming following anomia treatment in patients with aphasia post-stroke. In contrast, treatment-related changes in semantic and phonological naming errors were associated with modulation of posterior cortex, primarily in temporal lobe regions that in normal subjects are activated during picture naming. Parietal lobe modulation involving naming-related regions also predicted changes in phonemic paraphasias. The relationship between anomia treatment outcome and neurophysiological measures – baseline naming-related activation and CBF – was far less certain. Although the current study strongly implicates the left hemisphere in treated anomia recovery, further studies in this area are imperative to better appreciate the relationship between brain activation, neurophysiology, and frank cortical damage.

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Figure 1.

A lesion overlay map showing the distribution of brain damage (N=30). The color scale shows the extent of lesion overlap in different regions with an upper threshold showing regions where at least 10 patients had damage (shown in red).

Figure 2.

The following images detail the creation of our volumes of interest for one representative patient. Panel A delineates the areas marked as lesioned tissue (frank lesion plus three mm surround, to account for partial volume effects), as well as the perilesional masks (3–15 mm beyond the lesion) divided by lobe. Panel B illustrates the group-level functional activation pattern seen in our healthy control group (n=14) for the same naming task performed by the patients with aphasia. Panel C shows the final masks (lobes are not shown here for purposes of clarity) used as our volumes of interest: the intact residual language network, the perilesional areas, and the areas of overlap between the two.

Figure 3.

The relationships between treatment related changes in cortical activity and naming responses: A. Activation change in the perilesional frontal lobe and change in correct naming; B. Activation change in residual naming areas in the temporal lobe and change in semantic paraphasias; C. Activation change in residual naming areas in the temporal lobe and change in phonemic paraphasias.

Table 1

Patient biographical and diagnostic information.

No.	Gender	Age	MPO	WAB AQ/Aphasia Type	Lesion Size (in cc)
1	F	53	14	44.8/Broca's	35.7
2	F	41	40	79.1/Anomic	190.1
3	M	61	72	72.1/Broca's	130.5
4	M	77	24	40/Broca's	23.1
5	F	72	24	87.1/Anomic	43.6
6	F	33	24	31.8/Broca's	42.2
7	M	54	65	89.7/Anomic	92.9
8	M	73	350	27.5/Broca's	278.1
9	F	65	107	26.3/Broca's	84.1
10	M	59	9	79.6/Conduction	79.6
11	F	71	52	91.9/Anomic	78.0
12	F	75	18	93.5/Anomic	10.8
13	M	58	22	92/Anomic	63.0
14	F	63	12	57.4/Conduction	50.3
15	M	63	98	50.7/TCM	420.5
16	F	45	68	51.9/Broca's	116.7
17	F	81	13	67.8/Anomic	48.0
18	M	52	23	30.6/Wernicke's	223.1
19	F	56	291	86.2/Anomic	35.0
20	F	60	41	95.2/Anomic	7.7
21	M	59	28	92.1/Anomic	24.2
22	F	56	17	38.4/Broca's	222.2
23	F	48	10	31.3/Broca's	129.3
24	M	53	29	68.7/Broca's	175.5
25	F	79	6	58.2/Conduction	65.2
26	M	44	11	25.7/Broca's	212.5
27	M	58	45	47.6/Broca's	118.4
28	M	57	7	31.2/Wernicke's	31.0
29	F	60	9	17.2/Global	274.0

No.	Gender	Age	MPO	WAB AQ/Aphasia Type	Lesion Size (in cc)
30	M	50	6	32.7/Broca's	172.9

MPO = months post onset; TCM = transcortical motor aphasia;
WAB AQ = Western Aphasia Battery Aphasia Quotient.

Table 2

Relationships between pre-post brain measures and behavioral measures of change.

Full Model	Stepwise					
	Cortical Areas	R ²	F	p	Cortical Areas	R ² F p
ChgfmMRI	ACC					
	Overlap	.20	1.89	.160	Frontal	.18 5.27 .030
	Perilesional	.30	3.38	.035	Frontal	.16 5.09 .033
	Residual	.10	0.88	.464	None	-- -- --
SEM	Overlap	.15	1.31	.294	None	-- -- --
	Perilesional	.07	0.59	.625	None	-- -- --
	Residual	.30	3.32	.038	Temporal	.28 9.57 .005
PHON	Overlap	.34	3.93	.021	Temporal	.23 7.63 .011
	Perilesional	.11	1.00	.412	None	-- -- --
	Residual	.50	7.72	.001	Temporal, Parietal	.50 11.89 .0001
PrefmMRI	Cortical Areas	R ²	F	p	Cortical Areas	R ² F p
	ACC					
	Overlap	.22	2.11	.127	None	-- -- --
	Perilesional	.10	0.85	.480	None	-- -- --
	Residual	.02	0.16	.923	None	-- -- --
SEM	Overlap	.38	4.79	.010	None	-- -- --
	Perilesional	.25	2.61	.074	Frontal	.22 7.37 .012
	Residual	.11	0.99	.417	None	-- -- --
PHON	Overlap	.05	0.37	.772	None	-- -- --
	Perilesional	.00	0.00	1.00	None	-- -- --
	Residual	.03	0.26	.853	None	-- -- --
rCBF	Cortical Areas	R ²	F	p	Cortical Areas	R ² F p
	ACC					
	Overlap	.14	1.07	.383	None	-- -- --
	Perilesional	.05	0.35	.789	None	-- -- --
	Residual	.36	3.94	.022	None	-- -- --

Full Model		Stepwise			
ChgfMRI	Cortical Areas	R ²	F	p	
SEM	Overlap	.26	2.39	.099	None
	Perilesional	.19	1.66	.206	None
	Residual	.18	1.58	.224	None
PHON	Overlap	.19	1.52	.239	None
	Perilesional	.11	0.88	.467	None
	Residual	.14	1.09	.374	None

Statistically significant predictive models are indicated in bold.

Regression analyses showing the relationships between treatment-related change in naming (ACC = change in correct naming; SEM = change in semantic paraphasias; and PHON = change in phonemic paraphasias) and treatment-induced change in functional activation (ChgfMRI), pre-treatment functional activation (prefMRI), and regional cerebral blood flow (rCBF) in three volumes of interests (Overlap = overlapping perilesional and residual areas; Perilesional = perilesional cortex excluding residual naming areas; and Residual = residual naming areas excluding perilesional cortex).