NONFLUENT APHASIA: THE RELATIONSHIP BETWEEN DEGREE OF LEFT-HEMISPHERE LESION, HOMOLOGOUS BRAIN ACTIVITY, AND PERFORMANCE

By

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To my parents and wonderful family

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Little is known about the predictive value of degree of lesion on the reorganization of language function and recovery in aphasia. This study investigated whether degree of lesion in left-perisylvian regions of interest (ROIs) was associated with the amount of right-hemisphere homologous functional activity during word generation, and performance on the Boston Naming Test (BNT) and Western Aphasia Battery-Aphasia Quotient measures (WAB-AQ). Nineteen chronic, nonfluent aphasia patients received structural and functional MRI prior to an intention-based language treatment aiming to re-lateralize language functions to the right hemisphere. During imaging, patients performed an event-related category member generation task. Two independent raters scored the degree of lesion in the left hemisphere on a scale of 0 to 5 and correlated the ratings with the volume of functional activity in the right-hemisphere homologues and the BNT and WAB scores prior to treatment. There was no relationship between degree of lesion in the left hemisphere and the amount of functional activity in the right-hemisphere homologous structures. However, patients with a higher degree of lesion showed poorer performance on measures of fluency and repetition. The authors concluded that reorganization of language functions to the right-hemisphere homologous structures shown in the literature may

not be a universally applicable concept and that degree of lesion is marginally related to spontaneous speech and repetition abilities in this sample.

CHAPTER 1
INTRODUCTION

Reorganization of Language Functions in Aphasia

Even before the advent of functional imaging, scientists began to question the role of the right hemisphere in recovery from aphasia. In 1877, Barlow reported the case of an aphasic patient who recovered language functions following a lesion in Broca's area. The same patient later lost language abilities subsequent to a right-hemisphere stroke. Based on this case, Barlow suggested that right-hemisphere mechanisms were involved in the recovery of language functions in aphasia (Barlow, 1877). This claim has been supported by other studies indicating that language functions in aphasic patients become impaired when the right hemisphere is anesthetized during WADA tests (Kinsborne, 1971). Similarly, Basso and colleagues have reported cases in which neuropsychological test performance decreased in aphasic patients after subsequent right-hemisphere stroke (Basso, Gardelli, Grassi, & Mariotti, 1989). Hence the right hemisphere seems to play an important role in the recovery of language functions in some aphasia patients.

Current evidence regarding left and right-hemisphere contributions to language function in aphasia remains controversial. A number of studies have indicated that recovery of language function in aphasia is primarily involved with right-hemisphere activity (Abo et al., 2004; Crosson et al., 2005; Gold & Kertesz, 2000; Weiller et al., 1995), while others emphasize the importance of dominant perilesional activity in recovery (Breier et al., 2004; Cornelissen et al., 2003; Duffau, Bauchet, Lehericy, & Capelle, 2001; Leger et al., 2002; Miura et al., 1999; Seghier et al., 2001; Warburton, Price, Swinburn, & Wise, 1999). For example, using fMRI, one study investigated how brain activity during meaningful and meaningless stories changed with the patients' auditory sentence comprehension skills. The authors found that irrespective of lesion

site, performance on tests of auditory sentence comprehension was positively correlated with activation in the right lateral superior temporal region (Crinion & Price, 2005).

Other evidence supporting the involvement of right-hemisphere activity in recovery from aphasia has suggested that when a shift of language functions occurs, it is mainly reorganized to right-hemisphere structures homologous to damaged left-hemisphere areas (Lazar et al., 2000). For example, Weiller and colleagues demonstrated that patients who had recovered from Wernicke's aphasia, after damage to Wernicke's area, showed activity in the right-hemisphere homologue of Wernicke's area (Weiller et al., 1995). Similarly, Blank and colleagues showed that aphasic patients with lesions in the left pars opercularis (posterior part of Broca's area) had more pronounced activity in the right pars opercularis during a language production task than aphasic patients without left pars opercularis lesions and neurologically healthy control subjects (Blank, Bird, Turkheimer, & Wise, 2003).

Just as some investigators advocate that recovery from aphasia is enhanced when the right hemisphere takes over language functions from damaged left-hemisphere areas, others suggest that optimal recovery in aphasia is accompanied by reorganization to left-hemisphere perilesional areas (Cao, Vikingstad, George, Johnson, & Welch, 1999; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Karbe et al., 1998). Heiss and colleagues found that aphasia recovery, measured by a test of language comprehension, was correlated with the re-activation of perilesional left-hemisphere structures, and that poor recovery was associated with activity in certain areas of the right hemisphere (Heiss et al., 1997). Similarly, one study used repetitive transcranial magnetic stimulation (rTMS) to inactivate the right pars triangularis (analog to the anterior part of Broca's area) as a treatment for aphasia. They demonstrated that all of the patients who received the rTMS treatment showed improved language performance two months

after treatment, indicating that activity in right pars triangularis may have hindered recovery for patients included in the study (Martin et al., 2004). However, the same author also found that rTMS of the right pars opercularis (analog to the posterior part of Broca's area) decreased picture naming accuracy and increased response latencies (Naeser et al., 2002). These findings indicate that certain right-hemisphere structures may interfere with language functioning while others may actually facilitate it.

The previously reported findings raise the question of degree of lesion and its role in the re-organization of language functions in aphasia. It may be possible that aphasia patients with smaller lesions do not need to re-lateralize language functions to the right hemisphere, due to the preservation of key structures of the language network in the dominant hemisphere. However, patients with more severe left-hemisphere lesions may reorganize certain language functions to the non-dominant hemisphere because the dominant hemisphere may no longer be a viable substrate for recovery (Crosson et al., 2007). Parallel to this point of view, Heiss and Thiel proposed a hierarchy of recovery based on degree of lesion, where best recovery of function can be associated with the reactivation of the dominant hemisphere, which is only possible after small lesions that affect language areas of minor importance to the network. The next step in the hierarchy is the involvement of an intrahemispheric network concerning secondary centers of the dominant network, which may lead to satisfactory improvement. The authors finally suggested that a less efficient interhemispheric compensation mechanism involving the contralateral homologous areas is related to less efficient improvement and is dependent on the severity of the damage to network components that reduce transcallosal inhibition (Heiss & Thiel, 2006). If this is the case, aphasia patients with higher degree of lesion in specific left-hemisphere structures,

should exhibit more pronounced activity in the right hemisphere, specifically in the homologous structures, than those with less severe lesions.

The work of Blank and colleagues (2003) suggested that right-hemisphere areas are recruited during language production only when their left-hemisphere counterparts are damaged. They used positron emission tomography (PET) to study the language production of 14 former nonfluent aphasia patients who subsequently recovered the ability to speak spontaneously in sentences. Patients performed an everyday propositional speech task during imaging. The authors found that aphasia patients with lesions to the left pars opercularis showed more pronounced activity, during a narrative language task, than healthy controls and aphasic patients with little to no lesion in the left pars opercularis. Since the patients had already recovered language functions at the time of assessment, the authors suggested that the increased activity observed in the right pars opercularis was related to recovery from nonfluent aphasia. A major weakness in Blank's work is that they only tested their hypothesis for pars opercularis and did not take into account the degree of lesion and its potential impact on the amount of activity observed in the homologous structures. It is important to replicate and extend the work of Blank and colleagues to include more areas of the language network and determine if degree of lesion in specific regions is associated with the amount of homologous activity in the right hemisphere.

This study examined the relationship between degree of lesion in the left hemisphere and the amount of homologous right-hemisphere activity during word generation in nonfluent aphasia patients. It was hypothesized that patients with higher degree of lesion in anterior and posterior perisylvian regions of the language network would show more pronounced activity in the right-hemisphere homologous structures due to the diminished capacity of the dominant

hemisphere to provide the necessary substrates for recovery, thereby enhancing re-lateralization of language functions to the right-hemisphere homologous structures.

Degree of Lesion and Language Performance in Aphasia

Little research has examined the relationship between degree of left-hemisphere lesion and language performance in aphasia. The extant literature regarding lesion characteristics and aphasia recovery appears perplexing due to considerable variation with regard to the type of aphasia patients included in the samples, the employment of inconsistent inclusion criteria, and the vast array of behavioral language measures used to assess recovery. Most of the research in this area has focused on the relationship between lesion characteristics and aphasia type (Kreisler et al., 2000), or the behavioral predictors of recovery in aphasia, such as measures of language comprehension predicting greater treatment success (Naeser et al., 1998). Unfortunately, the literature has neglected to consistently address the relationship between degree of lesion in specific areas of the language network and performance on different language measures during recovery in nonfluent aphasia.

One study found that lesions in the posterior-superior-temporal and supramarginal regions were associated with poor auditory comprehension in a sample of 39 left-hemisphere stroke patients (Selnes, Knopman, Niccum, Rubens, & Larson, 1983). On the contrary, a different study found that lesions to Broca's and Wernicke's areas were not significantly related to language comprehension (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). The authors used voxel-based lesion symptom mapping (VLSM) to investigate the relationship between left-hemisphere damaged areas of 64 chronic stroke patients and performance on a measure of language comprehension. They found that the following left-hemisphere areas affected performance: the posterior middle temporal gyrus and underlying white matter, the anterior

superior temporal gyrus, the superior temporal sulcus and angular gyrus, mid-frontal cortex in Brodmann's area 46, and Broadmann's area 47 of the inferior frontal gyrus.

A subsequent study used VLSM on 50 aphasic patients to investigate the lesion correlates of conversational speech deficits. The authors found that damage to the anterior insula predicted low grammatical complexity and amount of speech produced. Additionally, the inferior frontal gyrus, sensorimotor and anterior temporal areas were also associated with lower scores on both grammatical complexity and amount of speech produced (Borovsky, Saygin, Bates, & Dronkers, 2007). Similarly, it has been reported that subjects with overall larger lesions showed less recovery of naming abilities while subjects with lesions in Wernicke's area and the inferior parietal cortex demonstrated the most severe naming impairment (Knopman, Selnes, Niccum, & Rubens, 1984).

In sum, the majority of studies have suggested that the intactness of posterior regions, especially Wernicke's area, is important for language recovery in aphasia. It is important to bear in mind that the current findings are inconsistent in terms of type and severity of aphasic disorder, procedures used to measure lesion size, brain areas included as regions of interest, and language measures used to assess improvement. Furthermore, individual cases have been reported which contradict most group findings (Basso & Farabola, 1997). Due to the inconsistent findings in the literature, more research is needed to better understand the relationship between degree of lesion and behavioral language measures associated with recovery of language functions in non-fluent aphasia.

The main purpose of this study was to expand the existent literature regarding the role of degree of lesion in the amount of functional homologous activity and language performance in nonfluent aphasia. One of the main goals was to attempt to replicate and extend the findings of

Blank and colleagues (Blank et al., 2003) to examine the relationship between degree of lesion in the left hemisphere and the amount of homologous right-hemisphere activity during word generation in chronic, nonfluent aphasia patients. Degree of lesion and homologous activity were measured in two broad regions of interest (ROIs): anterior (A) and posterior (P) perisylvian regions. The A ROI consisted of pars opercularis and pars triangularis, which together form Broca's area. The P ROI was comprised of the supramarginal gyrus, the angular gyrus, and the posterior third of the superior and inferior temporal gyri, which was labeled Wernicke's +. These areas were selected because they all serve different aspects of language function and have been associated with recovery in aphasia (Blank et al., 2003; Knopman et al., 1984; Martin et al., 2004; Selnes et al., 1983). For a detailed definition of the anatomical boundaries of each ROI, see Appendix C.

Another goal of this study was to examine the relationship between degree of lesion and language performance in nonfluent aphasia. As stated in the introduction, the literature remains inconclusive regarding the role of degree of lesion in language functions in nonfluent aphasia due to the variability of aphasia types included in the samples and the measures used to assess recovery. This study examined the relationship between degree of lesion in the A and P ROIs and performance in nonfluent aphasia using the Boston Naming Test [BNT] (Kaplan, Goodglass, & Weintraub, 1983) and the Western Aphasia Battery-Aphasia Quotient measures [WAB-AQ] (Kertesz, 1982).

Aim 1

To examine the relationship between left-hemisphere degree of lesion in the A and P ROIs and amount of right-hemisphere homologous activity during word generation in nonfluent aphasia.

Hypothesis 1: It was hypothesized that patients with higher degree of lesion in the A and P regions would show more pronounced activity in the right-hemisphere homologous structures of the same ROIs. More pronounced homologous activity may be due to the diminished capacity of the dominant hemisphere to provide the necessary substrates for recovery, thereby encouraging re-lateralization of language functions to the right-hemisphere homologous structures (Heiss & Thiel, 2006).

Aim 2

To examine the relationship between degree of lesion in the left-hemisphere A and P ROIs and language performance in nonfluent aphasia using the BNT and WAB-AQ measures.

Hypothesis 2: Due to the inconsistent literature regarding the relationship between degree of lesion and language performance in aphasia, exploratory analyses were carried out to investigate the role of degree of lesion in aphasia recovery using the BNT and WAB-AQ measures. It was hypothesized that higher degree of lesion in the A and P ROIs would be associated with lower scores on the BNT and WAB-AQ measures [spontaneous speech, comprehension, repetition, and naming] (Goldenberg & Spatt, 1994; Kertesz et al., 1993; M. Naeser et al., 1990).

CHAPTER 2
METHODS

Subjects

A subset of subjects from two larger aphasia treatment studies consisting of 19 patients with nonfluent aphasia was included in this sample. These studies (1 and 2) consisted of an intention-based language treatment for chronic nonfluent aphasia patients and aimed to re-lateralize language functions to the right medio-frontal hemisphere by asking subjects to initiate word production trials with a complex, non-symbolic left-hand gesture. Both samples did not differ significantly from each other on any variable, with exception of the degree of lesion in the P ROI, where study 1 had a mean posterior score of 3.38 (SD = 1.75) while study 2 had a mean posterior score of 6.55 (SD = 4.34) [$t(13.97) = -2.19$, $p < .05$]. The current study included data from pre treatment fMRI and language measures only, and therefore did not investigate changes in brain activity or language improvement from pre to post treatment.

Of the 19 patients, only 10 had usable fMRI images; therefore, data from 10 subjects was used to examine the relationship between degree of lesion and right-hemisphere homologous activity, while data from all 19 subjects was used to assess the relationship between degree of lesion and language performance. See Table 2-1 for subject demographics.

All subjects were recruited from the Brain Rehabilitation Research Center of the Malcom Randall VA Medical Center in Gainesville, FL, the Shands Health Care System, Brooks Rehabilitation Hospital in Jacksonville, FL, and the Gainesville and Jacksonville communities at large. All subjects had documented left-hemisphere lesions on clinical MRI or CT scans due to ischemic or hemorrhagic stroke. Subjects had no history of right-hemisphere stroke, learning disabilities, neurological conditions, or chronic substance abuse and were premorbidly right-handed and native English speakers. All subjects gave informed consent according to the

guidelines stipulated by the Internal Review Board (IRB) of the University of Florida Health Science Center.

Inclusion criteria: Non-fluency was defined by hesitations due to word-finding difficulty on a narrative speech sample elicited from the Boston Diagnostic Aphasia Examination's Cookie Theft Picture (Goodglass & Kaplan, 1983). Subjects also had minimally impaired comprehension at the single-word level and evidence of posterior inferior frontal lesion on MRI scans. All subjects were 6 or more months post onset of their most recent stroke and had no contraindications for MRI scanning, such as cardiac pacemaker, ferrous metal implants, or claustrophobia.

Word-finding difficulty was moderate to severe as indicated by scores of less than 48 and more than 3, out of 60 naming items, on the Boston Naming Test (Kaplan et al., 1983). To ensure that patients understood study instructions during the fMRI session, study 2 included only those patients with a score within two standard deviations from the age-appropriate mean for normal subjects on the Peabody Picture Vocabulary Test IV (Dunn & Dunn, 2007). See Table 2-1 for subject demographics.

Procedure

Structural and functional MRI and behavioral testing data (BNT and WAB) were obtained during the subject's pre-treatment scanning and testing sessions, respectively, which were usually less than one week apart. Even though a total of 19 subjects participated in fMRI and testing sessions, only 10 subjects had usable fMRI data.

Testing Session

A variety of behavioral measures were acquired as part of the protocol for the larger studies, however only those measures relevant to this particular study will be discussed.

All subjects were administered the BNT and the WAB-AQ subtests. The BNT is a confrontation naming test consisting of 60 items (Kaplan et al., 1983). Subjects attempted to name all 60 line drawings. For the final analyses the percent correct, out of 60 items, was employed. Subjects were also administered the Western Aphasia Battery (WAB) subtests necessary to calculate the Aphasia Quotient (AQ). This portion of the test was developed to assess the main clinical aspects of language function: content, fluency, auditory comprehension, repetition and naming. The aphasia quotient is an overall measure of aphasia severity which uses the oral portion of the WAB's language assessment (Kertesz, 1982). Subjects' WAB AQ, spontaneous speech, comprehension, repetition, and naming raw scores were entered into the analyses.

Imaging Task: Category Member Generation

The fMRI task used to examine the level of activity in right-hemisphere homologues of the A and P ROIs was an event-related overt word generation task. For study 2, participants saw and heard a category (e.g., "birds") and responded by saying aloud a single category member (e. g., "robin"). There were 6 runs of 10 category exemplars each for a total of 60 category-member generation trials. Each active trial lasted 13.6 seconds (8 TRs). The inter-trial intervals alternated between 13.6, 15.3, and 17 seconds in a pseudo random fashion, which allows adequate time for the hemodynamic responses of aphasic patients to return to baseline before the subsequent trial is initiated. Each run lasted 5 minutes, 16.2 seconds for a total fMRI sequence of 31.62 minutes. For study 1, the category member generation task consisted of 5 runs with 9 category exemplars each, for a total of 45 trials. Inter-trial intervals varied from 21.6, 23.2, 24.9, and 26.6 seconds and were randomized over the course of the runs. The categories for study 1 were presented auditorily only rather than audio-visually.

The auditory stimuli were presented via earphones of a Commander XG Audio System (Resonance Technology) built specifically for use in MRI environments. The visual stimuli, for study 2 only, were presented via a computer monitor mounted over the head coil (Eloquence systems). The category-member generation task was selected because previous studies in our laboratory have found that, compared to other language tasks; it optimizes activity in language-related areas including the ROIs selected in this study.

An Eloquence System (INVIVO) was used to program the experiment. It is equipped with E-Prime software to program experiments and record data. The output of the Eloquence computer was connected to the MRI Audio System for stimulus presentation. Subjects' verbal responses on word-generation tasks were recorded by connecting a Phone-Or dual channel fiber optic, noise-canceling microphone to a separate Dell laptop computer using Audition 1.5 (Adobe) software for subjects' responses to be scored off-line. Similarly, subject's responses were recorded with Cool Edit 2000 software to obtain response times off-line.

Image Acquisition

Since data were obtained from studies 1 and 2, structural and functional images were acquired using three different 3 Tesla scanners. Images for the subjects in study 1 (N = 8) were acquired on a GE 3T Signa LX scanner with a quadrature radio frequency coil, or on a Siemens Allegra 3T scanner. Thirty-two contiguous sagittal slices covering whole brain were acquired using a 1-shot spiral sequence (TR = 1660 ms; TE = 18 ms; 70° flip angle; 64x64 matrix; FOV = 200 mm; 4 mm in thickness). An additional 6 images (9.96 seconds) were added to the beginning of each functional run to allow for homogeneity of the MR signal. A structural T1-weighted spoiled gradient-recalled acquisition in the steady state (GRASS) sequence was obtained for localization purposes and to determine the degree of lesion in the left-hemisphere ROIs (TR = 23

ms; TE = 6 ms; 25° flip angle; 256x192 matrix; 1.3 mm in thickness; 124 slices; FOV = 240 mm). Foam padding was used to limit head motion during scanning.

All images for study 2 (N = 11) were acquired on a Philips 3 Tesla whole body scanner at the McKnight Brain Institute of the University of Florida. For functional MRI, the whole brain was imaged in 1.7 seconds using a gradient echo planar sequence with 36 x 4 mm thick sagittal slices (TR = 1700 ms; TE = 30 ms; FA = 70 degrees; FOV = 24 cm, matrix = 64 x 64). Prior to collecting functional images, high-resolution T1-weighted structural images were acquired for 160 x 1 mm thick sagittal slices using TFE acquisition (TE = 3.7 ms; TR = 8.1 ms; FOV = 24 cm; FA = 8 degrees; matrix size = 240 x 240). The T1-weigthed images were used to assess the degree of lesion in the left-hemisphere ROIs using a rating scale from 0-5, while the functional images were used to obtain the number of active voxels on each of the right-hemisphere homologous ROIs.

Image Analyses

Images were analyzed on a Linux workstation (Dell) using Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). To reduce effects of head motion, the 3-dimensional volume registration option in AFNI was used to spatially register images from each run to the first image of the first functional run, because its acquisition immediately follows acquisition of T1-weigthed anatomic images onto which functional images are overlaid. All voxels in which the standard deviation (SD) of acquired time series exceeded 8% of the mean signal intensity was set to zero to minimize large vessel effects and other artifacts. Individual imaging runs were orthogonalized for linear trends and then concatenated into a single time series. Due to residual motion artifacts produced by overt language production in the scanner, functional images were detrended for motion artifacts using a refinement of the procedure developed by Gopinath and

colleagues (Gopinath et al., in press). Analyses included all trials in which a participant attempted a spoken response.

Hemodynamic responses (HDRs) for word-generation trials were modeled as a single HDR using the deconvolution program in AFNI. Deconvolution makes no a priori assumptions about the shape of the HDR, but rather derives it empirically. In deconvolution, an estimate of the HDR is deconvolved from the acquired time series in each voxel; then, the estimated HDR is convolved with the temporal sequence of trials and tested for goodness of fit with the original time series. If a brain region is actively involved in the task, the deconvolution produces an estimated response that has high and consistent amplitude and a good fit with the time series. Goodness of fit between the acquired series and the estimated time series based on deconvoltuion is tested using R^2.

Two types of deconvolution were performed for functional image analysis. First, in the response-based deconvolution, modeling of HDRs for each trial in which a spoken response is given commences one image prior to the image during which the response was given and is modeled for 16 images. Modeling the HDR beginning 1 image prior to spoken response onset allows us to see the onset of responses in areas whose activity leads up to the response; a 27 sec time course is necessary to capture delayed effects that may occur for some participants. In the second, stimulus-based deconvolution, modeling of the HDR commenced at presentation of the stimulus and included 16 images. Because the interval between stimulus onset and response can vary by as much as 4 images within a single subject, HDRs in areas whose activity is more closely associated with stimulus onset can be visualized with greater sensitivity using the stimulus-based deconvolution. In some subjects, this deconvolution adds information about frontal activity, probably because some retrieval processes can begin soon after stimulus onset.

A single statistical parametric map was created in which each voxel contained the highest of the R^2 values derived from the response-based or the stimulus-based deconvolution. To equate for sensitivity across the three different scanners used to acquire images, the top 1% of activity for each subject was used to determine if a brain voxel showed a task-related HDR; therefore the threshold of R^2 differed by subject. Similarly, to correct for brain size, the total number of active voxels per ROI was divided by the total amount of brain voxels for each subject.

To obtain the right-hemisphere homologous activity, masks were drawn over each right-hemisphere ROI using the draw dataset function of AFNI. Subsequently, the number of active voxels under each of the masks was obtained and entered into the analyses. Each area comprising the broad ROIs was drawn separately in order to assess their individual relationship to degree of lesion. Five masks were drawn in the right hemisphere: pars opercularis (Pop), pars triangularis (Ptr), angular gyrus (AG), supramarginal gyrus (SMG), and the posterior third of the superior and middle temporal gyri (W+), see Table 2-2 for ROI names and abbreviations. The number of active voxels in Pop and Ptr was summed to derive at the total number of active voxels for the A ROI, while the number of active voxels for AG, SMG, and W+ were summed to obtain the total number of active voxels in the P ROI. For a detailed listing of the anatomical boundaries used to define each ROI see Appendix C.

Lesion Analysis

To determine degree of lesion for each left-hemisphere ROI, a modification of a lesion analysis procedure based on Naeser and colleagues was used (Naeser et al., 1998). The Naeser scale has been validated by Naeser and colleagues in several published articles and consists of the following ratings: 0 = no lesion; 1 = equivocal lesion; 2 = small, patchy or partial lesion; 2.5 = patchy, less than half of area has lesion; 3 = half of area has lesion; 4 = more than half of area has solid lesion; 5 = total area has solid lesion (Naeser, Palumbo, Helm-Estabrooks, Stiassny-

Eder, & Martin, 1989). Two trained raters scored the brains separately using the high resolution T1-weighted scans for each subject. Both raters were blinded to the subject's identity and scores on behavioral measures.

Prior to rating the subject's lesions, inter-rater reliability was established using a set of four practice brains. The practice brains were from left-hemisphere stroke patients who had participated in a different study conducted in our laboratory. The scans were high resolution T1 – weighted images and the same rating procedures as described below were followed. After rating each practice set independently, the raters met to discuss any discrepancies before rating the next practice set. The correlation between the two sets of ratings for all four scans was $r = .903$, $p < .001$.

To prepare the images for lesion scoring, the anterior and posterior commissure (ac-pc) were aligned using the define markers function on AFNI so they are in the same plane. Once each brain was ac-pc aligned, the raters independently scored each ROI using the rating scale in Appendix A.

The first lesion scoring step was to anatomically define each of the ROIs using AFNI. The ROIs were structurally defined based on sulcal anatomy. An atlas of sulcal anatomy was referenced to accurately define each ROI and identify inter-individual sulcal variation patterns (Ono, Kubik, & Abernathey, 1990). The templates developed by Damasio were also used for reference to help identify the ROIs (Damasio, 1995). For a list of ROI definitions see Appendix C.

Each ROI was defined and rated separately by the areas that comprised them. For example, the A ROI was rated as the summed scores for Pop and Ptr. Similarly, the P ROI rating was

derived from the summed ratings for AG, SMG, and W+. See Table 2-2 for a list of ROI names and abbreviations.

After each rater anatomically defined the 5 ROIs, they were drawn using the draw dataset function of AFNI in order to identify each ROI if discrepancies between raters occurred. The slice numbers where an ROI began and ended were noted on a scoring sheet (see Appendix B). Subsequently, the two raters independently assessed the extent of lesion, slice by slice, assigning a score of 0 through 5 on every slice of each ROI based on the rating scale in Appendix A. Once each ROI was scored slice by slice, a global lesion score was assigned as the total extent of the lesion for each ROI ranging from 0 through 5 (same criteria as listed above). The global lesion score was based on the slice by slice ratings and the relative size of the lesion on each slice, but was not derived from averaging the individual slices scores.

After the raters independently determined each ROI's global lesion score, the global scores were compared. Ratings that differed by one point or less were averaged and used in the analyses. If a global rating differed by more than one point, the raters discussed and modified them until the 2 scores differed by one point or less, after which they were averaged. When discussing rating discrepancies, the raters referred to the slice by slice ratings to see how they arrived at the global lesion score. Only the global lesion scores were entered into the statistical analyses.

Statistical Analyses

Analysis 1

To examine the relationship between degree of lesion and right-hemisphere homologous activity, two-tailed Spearman correlations were conducted to identify significant relationships at the $p < .05$ probability level. Spearman correlations were conducted because some of the variables included in the analysis were not normally distributed. The following variables were

correlated: degree of left-hemisphere lesion scores for the A and P ROIs and the number of active voxels in the right-hemisphere A and P ROIs during category member generation.

Analysis 2

To examine the relationship between degree of lesion and language performance, two-tailed Spearman correlations were performed between the A and P degree of lesion scores and the BNT and WAB-AQ components. Due to the inconsistent relationships reported in the literature between extent of lesion and language performance, these correlations were considered exploratory in nature.

Table 2-1. Subject demographics (N=19)

	Mean (SD)	Minimum	Maximum
Age	66.9 (12)	48	92
Education	13.4 (1.9)	12	18
Months since stroke	45.5 (51.9)	8	207

Notes: Ten subjects were male and 9 female; 18 were Caucasian and 1 was African American.

Table 2-2. ROI names and abbreviations

	Anterior (A) ROI	Posterior (P) ROI
Pars opercularis (Pop)	X	
Pars triangularis (Ptr)	X	
Angular gyrus (AG)		X
Supramarginal gyrus (SMG)		X
Wernicke's + (W+)		X

CHAPTER 3
RESULTS

Due to the unavailability of fMRI data for 9 out of 19 subjects included in this study, the sample sizes differed by specific aim. That is, data included in the analyses examining the association between degree of lesion and functional activity in the homologous right-hemisphere structures (Aim 1) consisted of only 10 subjects. Data included in the analyses for Aim 2 included a sample size of 19 subjects. Given the small sample size and the number of comparisons performed during analyses, there was an increased risk of making a Type I error. All comparisons were corrected for family-wise error using Bonferroni corrections. Furthermore, since some of the variables included in the analyses were not normally distributed, Spearman's rho correlations for rank-level data were conducted.

To provide context for the statistical analyses that were conducted in this study, Table 3-1 provides descriptive information for the fMRI activity in homologous structures of the right hemisphere during the word generation task. Table 3-2 shows the mean and standard deviations of the lesion ratings for each ROI. Table 3-3 shows the individual lesion scores for each of the 19 subjects. Table 3-4 shows the mean and standard deviations for the language measures used to assess performance.

Results for Aim 1

It was hypothesized that patients with higher degree of lesions in the A and P regions would show more pronounced activity in right-hemisphere homologous structures due to the diminished capacity of the dominant hemisphere to provide the necessary substrates for recovery, thereby facilitating re-lateralization of language functions to the right-hemisphere homologous structures (Heiss & Thiel, 2006).

Two-tailed Spearman correlations of left-hemisphere degree of lesion and homologous right-hemisphere activity revealed no significant relationships. Neither the A ROI (*Spearman's rho* = .20, p = .57) nor the P ROI (*Spearman's rho* = -.18, p = .63) degree of lesion scores were associated with their homologous functional activity during the category member generation task. It is important to keep in mind that the sample size for this analysis was only 10 subjects, thus power to detect significant relationships was greatly diminished. See Table 3-1 for correlation values.

When examining the relationship between the homologous activity of the A and P ROIs to the BNT and WAB-AQ measures, activity in the A ROI was negatively related to the WAB comprehension measures (*Spearman's rho* = -.71, $p < .05$). This relationship was no longer significant after correcting for multiple comparisons. When decomposing each ROI into its respective components, the amount of activity in the right-hemisphere Pop (*Spearman's rho* = -.69, $p < .05$) and AG (*Spearman's rho* = -.68, $p < .05$) was negatively related to the WAB comprehension measures, while activity in the SMG was positively associated with the WAB-AQ (*Spearman's rho* = .63, $p = .05$) and repetition scores (*Spearman's rho* = .79, $p < .01$). These associations were no longer significant after applying Bonferroni corrections for multiple comparisons. These findings indicate that homologous activity in certain structures may be beneficial for performance (SMG), while activity in others may affect it (A ROI, Pop, AG). In addition, when examining the relationship between the degree of lesion for each component of the A and P ROIs to their corresponding degree of activity in the right hemisphere, no significant relationships were revealed. Table 3-6 shows the values of the correlations between homologous brain activity and behavioral language measures for the sample of 10 nonfluent aphasia patients who had usable fMRI data.

Results for Aim 2

It was hypothesized that higher degree of lesion in the A and P ROIs would be associated with lower scores on the BNT and WAB-AQ measures (spontaneous speech, comprehension, repetition, and naming). When using the larger sample (N=19), Spearman correlations between degree of lesion and performance on the BNT and WAB-AQ measures revealed no significant associations, after Bonferroni corrections, for either the A or the P ROIs. Prior to correcting for multiple comparisons, the P ROI lesion score was marginally associated with WAB repetition performance (*Spearman's rho* = -.45, $p = .06$).

Nevertheless, when decomposing the A and P ROIs into the individual areas that comprised them, Ptr lesion score was negatively associated with WAB spontaneous speech score (*Spearman's rho* = -.50, $p < .05$). Similarly, AG (*Spearman's rho* = -.48, $p < .05$) and SMG lesion scores (*Spearman's rho* = -.51, $p < .05$) were negatively associated with the WAB repetition score prior to Bonferroni corrections. These marginal associations indicate that, at the individual ROI level, a greater degree of lesion is associated with poor performance. More specifically, anterior regions (Ptr) are associated with nonfluency, while a greater degree of lesion in posterior perisylvian areas (AG & SMG) is associated with poorer repetition ability. For a listing of correlations between degree of lesion and the BNT and WAB-AQ measures see Table 3-7. Refer to Tables 3-2 through 3-5 for descriptive information regarding lesion scores, activity levels, and behavioral performance.

Table 3-1. Correlations between Anterior and Posterior ROI lesion scores and homologous activity (N = 10)

	Anterior score	Anterior activity	Posterior score	Posterior activity
Anterior score	1	0.2	0	-0.07
Anterior activity	0.2	1	-0.09	0.07
Posterior score	0	-0.09	1	-0.18
Posterior activity	-0.07	0.07	-0.18	1

Notes: Two-tailed Spearman's correlations. None were significant. Functional activity was derived from the right-hemisphere homologous ROIs during category member generation task. Anterior ROI = sum of pars triangularis and pars opercularis. Posterior ROI = sum of angular gyrus, supramarginal gyrus, and wernicke's +.

Table 3-2. Number of right-hemisphere active voxels (N = 10)

	Mean	SD	Minimum	Maximum
Anterior ROI	399.3	949.2	29	3090
Posterior ROI	453.4	349.71	64	1261
Pars opercularis	223.51	550.65	0	1788.12
Pars triangularis	175.76	400.41	0	1301.52
Angular gyrus	35	33.65	0	89.16
Supramarginal gyrus	31.06	30.27	0	83.9
Wernicke's +	387.44	348.84	43.48	1227.95

Notes: Functional activity was derived from the right-hemisphere homologous structures during category member generation task. Anterior ROI = sum of pars triangularis and pars opercularis. Posterior ROI = sum of angular gyrus, supramarginal gyrus, and wernicke's +.

Table 3-3. Left-hemisphere lesion ratings (N= 19)

	Mean	SD	Minimum	Maximum
Anterior ROI	4.55	3.55	0	10
Posterior ROI	5.21	3.77	0	11.5
Pars opercularis (Pop)	2.83	1.74	0	5
Pars triangularis (Ptr)	1.72	2.08	0	5
Angular gyrus (AG)	1.32	1.33	0	4
Supramarginal gyrus (SMG)	2.26	1.55	0	4.5
Wernicke's + (W+)	1.63	1.52	0	4.5

Notes: Descriptives for each left-hemisphere ROI. Anterior ROI = sum of Pop and Ptr. Posterior ROI = sum of AG, SMG, and W+. Maximum lesion rating for Anterior ROI = 10 (5x2). Maximum lesion rating for Posterior ROI = 15 (5x3).

Table 3-4. Individual lesion ratings

Subject	Anterior ROI	Posterior ROI	Pop	Ptr	AG	SMG	W+
1	9	2.5	4.5	4.5	0.5	2	0
2	10	6.5	5	5	1	4.5	1
4	5.5	1	4	1.5	0	1	0
5	4	4.5	4	0	1	2.5	1
6	5.5	4.5	4	1.5	0	2	2.5
7	0	0.5	0	0	0	0	0.5
8	1.5	11.5	1.5	0	4	3.5	4
9	0	8.25	0	0	2.75	4	1.5
10	2.5	0	2.5	0	0	0	0
11	5.5	1	2.75	2.75	0	0	1
12	3.5	9	3	0.5	2	3.5	3.5
13	10	8.25	5	5	2.25	4.5	1.5
14	0.5	11.5	0.5	0	3.5	3.5	4.5
15	7.5	10	3	4.5	2.5	3.5	4
16	2	7.5	2	0	2.5	2.5	2.5
17	3	2.5	3	0	0	2.5	0
18	10	3.5	5	5	1	2.5	0
19	0	4.5	0	0	2	0	2.5
21	6.5	2	4	2.5	0	1	1

Notes: Degree of lesion ratings for each of the 19 subjects included in the study. Individual ROI scores are the averaged global scores of each rater. Anterior degree of lesion was calculated as the summed scores of Pop and Ptr (Broca's Area). The posterior degree of lesion was calculated as the summed scores of AG, SMG and W+. Pop = pars opercularis; Ptr = pars triangularis; AG = angular gyrus; SMG = supramarginal gyrus; W+ = wernicke's plus.

Table 3-5. Behavioral language measures (N = 19)

	Mean	SD	Minimum	Maximum
BNT % correct	0.44	0.21	0.13	0.83
WAB Aphasia Quotient	67.31	11.38	45.4	81.9
WAB spontaneous speech	12.26	3.02	7	16
WAB comprehension	170.26	15.50	135	200
WAB repetition	61.42	22.85	24	98
WAB naming	67.32	16.17	31	92

Notes: Scores on the BNT were expressed as percent correct (out of 60 items) while scores on the WAB were expressed as the raw scores for each component of the AQ. Higher scores indicate better performance. BNT = Boston Naming Test; WAB = Western Aphasia Battery.

Table 3-6. Correlations between ROIs, homologous activity, and language performance (N = 10)

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Pop score	1									
2. Pop activity	0.20	1								
3. Ptr score	0.80**	0.22	1							
4. Ptr activity	-0.01	0.69*	0.02	1						
5. AG score	-0.05	-0.24	-0.18	-0.56	1					
6. AG activity	0.25	0.47	0.54	0.63	-0.56	1				
7. SMG score	0.26	-0.18	0.12	-0.44	0.86**	-0.23	1			
8. SMG activity	-0.02	-0.21	-0.22	-0.21	-0.33	-0.49	-0.53	1		
9. W+ score	-0.25	0.34	-0.20	0.07	0.54	-0.06	0.56	-0.54	1	
10. W+ activity	-0.20	0.08	-0.01	-0.12	-0.10	-0.12	-0.32	0.51	-0.01	1
11. BNT % correct	0.32	0.18	0.01	0.13	-0.24	-0.15	-0.05	0.41	0.03	-0.18
12. WAB Aphasia Quotient	0.10	0.02	-0.12	-0.08	-0.27	-0.37	-0.26	0.63*	-0.13	-0.04
13. WAB spontaneous speech	0.17	0.41	-0.09	0.31	-0.38	-0.08	-0.29	0.31	0.01	-0.31
14. WAB comprehension	-0.37	-0.69*	-0.52	-0.47	0.08	-0.68*	-0.06	0.60	-0.13	0.12
15. WAB repetition	-0.13	0.05	-0.37	0.16	-0.51	-0.23	-0.54	0.79**	-0.26	0.24
16. WAB naming	0.18	0.10	0.40	-0.16	-0.35	0.05	-0.31	0.16	-0.17	-0.10

Notes: Two-tailed Spearman's correlations between individual ROIs, right-hemisphere homologous activity, and behavioral language measures. * Correlation is significant at the .05 level. ** Correlation is significant at the .01 level. All correlations were no longer significant following family-wise Bonferroni corrections (required $p < .01$ for significance on correlations between ROI lesion scores and homologous activity; required $p < .001$ for significance on correlations between lesion scores, homologous activity and language performance measures). Pop = pars opercularis; Ptr = pars triangularis; AG = angular gyrus; SMG = supramarginal gyrus; W+ = wernicke's plus; BNT = Boston Naming Test; WAB = Western Aphasia Battery.

Table 3-7. Correlations between lesion scores and language performance (N = 19)

	1	**2**	**3**	**4**	**5**	**6**	**7**
1. Anterior score	1						
2. Posterior score	-0.08	1					
3. Pop score	0.94**	-0.11	1				
4. Ptr score	0.93**	-0.03	0.81**	1			
5. AG score	-0.23	0.91**	-0.28	-0.15	1		
6. SMG score	0.23	0.82**	0.25	0.23	0.71**	1	
7. W+ score	-0.30	0.84**	-0.39	-0.19	0.74**	0.45	1
8. BNT % correct	0.09	-0.03	0.10	-0.02	-0.12	-0.01	-0.01
9. WAB Aphasia Quotient	-0.26	-0.37	-0.20	-0.42	-0.41	-0.45	-0.20
10. WAB spontaneous speech	-0.32	-0.18	-0.21	-0.50*	-0.25	-0.41	0.04
11. WAB comprehension	-0.01	-0.07	-0.05	-0.11	0.04	0.11	-0.14
12. WAB repetition	-0.13	-0.45*	-0.15	-0.24	-0.48*	-0.51*	-0.23
13. WAB naming	-0.11	-0.15	-0.08	-0.14	-0.23	-0.18	-0.12

Notes: Two-tailed spearman correlations between degree of lesion scores and behavioral language measures. * Correlation is significant at the .05 level. ** Correlation is significant at the .01 level. All correlations were no longer significant following family-wise Bonferroni corrections (required $p < .001$ for significance). Pop = pars opercularis; Ptr = pars triangularis; AG = angular gyrus; SMG = supramarginal gyrus; W+ = wernicke's plus; BNT = Boston Naming Test; WAB = Western Aphasia Battery.

CHAPTER 4
DISCUSSION

This chapter reviews the major findings of the current study and discusses their theoretical implications. It also focuses on discussing the limitations of the current study and suggests future directions to expand the field of lesion analysis and recovery from aphasia. It is important to restate that the current study had a relatively small sample size (N=19), and therefore the results should be interpreted with caution.

Review of Findings

Review of Aim 1

It was expected that patients with higher degree of lesions in the A and P regions would show more pronounced activity in right-hemisphere homologous structures due to the diminished capacity of the dominant hemisphere to provide the necessary substrates for recovery, thereby facilitating re-lateralization of language functions to the right-hemisphere homologous structures (Heiss & Thiel, 2006). Results indicated that there was no association between degree of lesion and the amount of right-hemisphere homologous activity in the A and P ROIs. Therefore, the current study was unable to replicate and extend the work of Blank and colleagues (Blank et al., 2003), suggesting that right-hemisphere structures (pars opercularis) show more pronounced activity only when their left-hemisphere counterparts are damaged. There are two possible explanations for why the current study could not replicate Blank's findings: (1) sample characteristics and (2) imaging task. Blank's sample consisted of 14 previous nonfluent aphasia patients who had recovered the ability to speak spontaneously in sentences, while the current study included subjects who were currently nonfluent. Moreover, Blank used PET to image language functions by having subjects respond to an autobiographical question such as "tell me what you like to do on a holiday," while the current study implemented a category member word

generation task, which may activate different areas of the language network. The fact that the samples and imaging tasks were so different could have affected the results of the current study. Similarly, it is possible that the use of three different 3T scanners to collect data added significant error variance due to differential sensitivity to blood-oxygen-level dependent (BOLD) changes.

On the other hand, when analyses of each of the 5 regions that comprised the A and P ROIs were examined, the amount of functional activity in the right-hemisphere SMG was positively associated with the WAB-AQ and repetition scores, indicating that more pronounced right-hemisphere activity in the SMG was related to less severe aphasia and better repetition abilities. These findings are inline with previous studies suggesting that right-hemisphere activity may help to compensate for the loss of language functions during rehabilitation in aphasia (Crinion & Price, 2005). In contrast, activity in right Pop and AG was negatively related to WAB comprehension scores indicating that more pronounced activity in these right-hemisphere structures was detrimental to performance on comprehension abilities. These results are similar to previous findings suggesting that heightened right-hemisphere activity in some structures can hinder recovery in nonfluent aphasia patients rather than enhancing it (Martin et al., 2004).

The overall findings point to the importance that damage to certain left-hemisphere structures plays in language performance for nonfluent aphasia. They also suggest that there is a beneficial role that certain right-hemisphere structures (such as the SMG) may play in the performance of different aspects of language functioning. Although the main hypothesis was not supported, the marginal relationships mentioned above revealed that functional activity in specific regions of the right hemisphere was related to both good and poor performance on language tasks.

In sum, these findings revealed the complexity of the relationship between lesion patterns, right-hemisphere activity, and language performance in aphasia that have been previously observed in the literature (Crinion & Leff, 2007; Crosson et al., 2007) and suggest that, while posterior right-hemisphere activity may enhance performance on repetition and mitigate overall aphasia severity, activity in neighboring structures might be detrimental to recovery of auditory comprehension. It can be concluded that Blank's findings are not universal and cannot be applied to this sample.

Review of Aim 2

It was expected that higher degree of lesion in the A and P ROIs would be associated with lower scores on the BNT and WAB-AQ measures (spontaneous speech, comprehension, repetition, and naming). Results revealed marginally significant relationships between anterior areas and overall fluency scores and posterior regions and repetition abilities, all of which indicated that more severe lesions were related to poorer performance. More damaged Ptr was related to worse performance on spontaneous speech, consistent with previous literature suggesting that speech production is related to more left frontal activity, which indeed necessitates more intact structures to function properly (Crinion & Leff, 2007).

Angular gyrus and SMG, both structures of the inferior parietal lobule, have previously been linked to language performance in aphasia (Kertesz et al., 1993), which was supported by this study since higher degree of lesion in these two areas was associated with poorer repetition abilities.

Although many studies have reported relationships between lesion characteristics and specific language deficits, others have argued that lesion-deficit analysis is an "uncertain method of defining the location of the neural sub-systems involved in language processing" (Wise, 2003) due to the variability of cortical organization of the language network at the individual level, and

the fact that damage resulting from stroke is extremely different from person to person, where damage to cortex, white matter, and subcortical structures vary greatly. Subjects in this study had very different lesions. Some lesions were large and solid; others were small and patchy, while some subjects had a greater degree of lesion in the anterior than posterior regions or vice versa. It is possible that different results could have been obtained if the current study included subjects with very similar lesion characteristics, in which case inferences regarding specific deficits could have been more transparent.

In sum, only marginal relationships were found between degree of lesion and performance on different language measures. This may be attributed to the variability of lesion distributions included in this sample which can affect the connections between different areas of the language network for some subjects and not others, thus obscuring the relationship between location and degree of lesion and specific deficit.

Study Implications

As stated earlier, the literature is mixed with regards to the relationship between left and right-hemisphere activity and language performance in aphasia. Some studies have been conducted that investigated this relationship; however, they have included different types of aphasia syndromes which makes it difficult to generalize the findings to nonfluent aphasia patients. When scientists better understand the reorganization of language functions in aphasia and how it relates to lesion characteristics and recovery of language functions, they will be better equipped to develop rehabilitation treatments that target the re-activation of either left or right-hemisphere structures while decreasing activity considered detrimental for recovery. This study was unable to determine the relationship between degree of lesion and right-hemisphere activity in the homologous structures of damaged left-hemisphere areas; however a larger sample with more circumscribed lesion distributions could shed much needed light into this relationship.

Similarly, it is crucial to better understand the lesion correlates of specific language deficits to advance our understanding of the neural substrates of language production in nonfluent aphasia. Better understanding of this relationship could aid therapists in predicting what kinds of deficits to expect from specific lesion patterns, and how these patterns can predict both spontaneous and treatment-induced recovery. If therapists can predict the lesion patterns associated with recovery from specific therapies, they will be better able to maximize recovery and minimize health care costs by selecting treatments with a higher probability of success in patients with specific lesion patterns and associated deficits.

Study Limitations

There were several limitations to this study. First and foremost, the sample size for Aim 1 consisted of only 10 subjects who had available fMRI data at the time the analyses were conducted. Small samples decrease statistical power to detect significant relationships above chance levels. A second limitation of this study was that the subjects' data were collected from two slightly different studies. There were 8 subjects from study 1 and 11 from study 2.

Another aspect that differed between studies 1 and 2 was the presentation of the stimuli during the fMRI task, which could have affected functional activity patterns in the right hemisphere. Both studies used the same imaging task (category member generation); however study 1 presented the stimuli auditorily, while stimuli presentation for study 2 was audio-visual. Moreover, structural and functional data were acquired using three different 3T scanners, which could have affected the sensitivity to detect task-related brain changes by study. To equate for sensitivity across the three scanners, only the top 1% of task-related functional activity for each subject was analyzed.

A third limitation of this study was that it did not examine the connectivity between areas of the language network, which is important to the reactivation of structures involved in

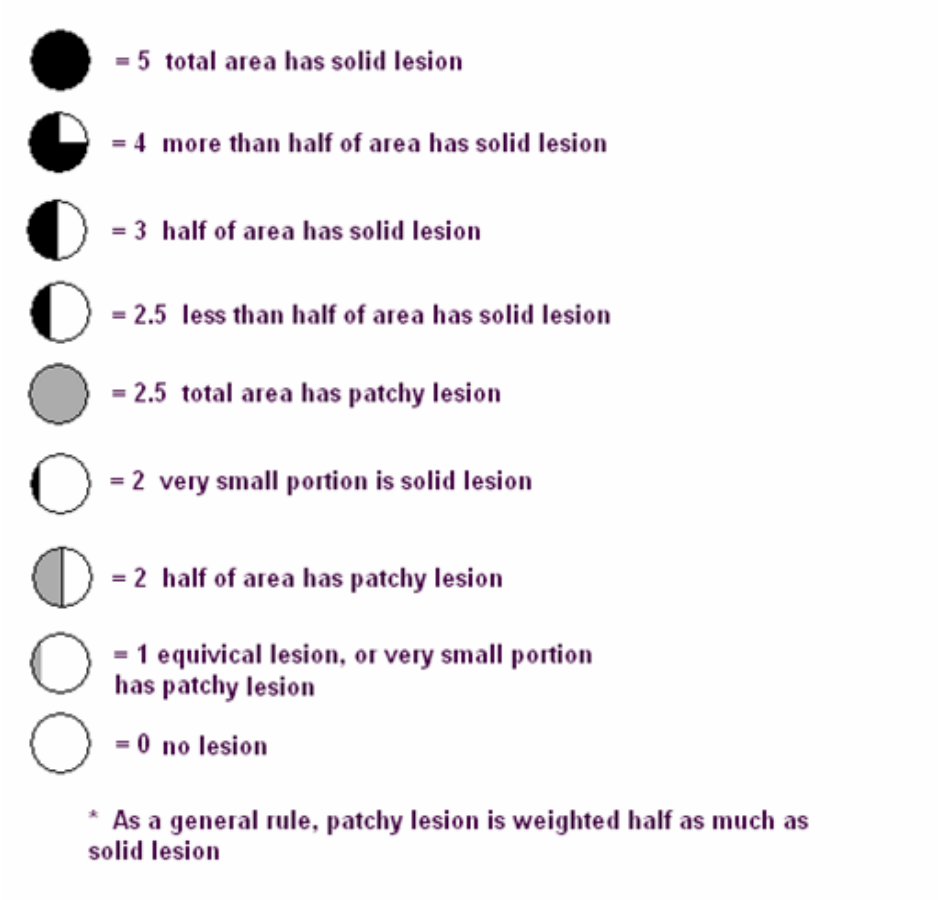
recovery, especially since damage from stroke is so variable and may include white matter lesions in certain subjects and not others, thus causing different behavioral deficits (Wise, 2003).

Future Directions

The study of recovery in aphasia is complex and remains poorly understood. To further investigate the relationship between degree of lesion, right-hemisphere activity, and related deficits, longitudinal studies including only one aphasia syndrome, similar behavioral deficits, and circumscribed lesion characteristics should be undertaken. Conducting such a study would likely be arduous due to the inter-individual variability of lesion characteristic and related deficits observed after stroke. Ideally, treatment studies will be carried out which take into consideration lesion characteristics, functional activity, and behavioral deficits before and after language treatment, as well as at long-term follow-up to measure the longevity of effects.

Furthermore, future studies should examine the integrity of white matter pathways connecting areas of the language network to one another to further understand the reorganization of language functions after stroke. Techniques such as diffusion tensor imaging (DTI) can be implemented in conjunction with fMRI to examine the connectivity between functional areas of the language network as well as assessing changes in white matter integrity over the course of treatment and their relation to functional reorganization (Bihan et al., 2001). Conducting such a study may prove a monumental task, but it would provide much needed information regarding recovery in aphasia and potentially aid in the development and implementation of novel treatments aiming to enhance recovery in patients with specific deficits and lesion characteristics.

APPENDIX A
DEGREE OF LESION RATING SCALE



APPENDIX B
DEGREE OF LESION SCORING SHEET

MRI Lesion Rating Sheet																
Subject:		Rating system														
Date:		0 = no lesion														
Scored By:		1 = equivocal lesion														
		2 = small, patchy or partial lesion														
		2.5 = patchy, less than half of the area has lesion														
		3 = half of area has lesion														
		4 = more than half of area has solid lesion														
		5 = total area has solid lesion														
ROI's																Global Score
Pars opercularis	Slice# L:															
	Score L:															
	Slice# R:															
Pars triangularis	Slice# L:															
	Score L:															
	Slice# R:															
Angular Gyrus	Slice# L:															
	Score L:															
	Slice# R:															
Supramarginal Gyrus	Slice# L:															
	Score L:															
	Slice# R:															
Wernicke's +	Slice# L:															
	Score L:															
	Slice# R:															

APPENDIX C
ROI DEFINITIONS

1) <u>Pars Opercularis (Pop)/ BA 44:</u>
• Anterior border = anterior ascending ramus of the sylvian fissure
• Posterior border = inferior precentral sulcus (anterior subcentral sulcus)
• Superior border = inferior frontal sulcus
• Inferior border = main branch of the sylvian fissure
• In the depth of the sylvian fissure it borders on the insula.

2) <u>Pars Triangularis (Ptr)/ BA 45:</u>
• Anterior/superior border = inferior frontal sulcus
• Posterior border = anterior ascending ramus of the Sylvian fissure
• Inferior border = anterior horizontal ramus and the sylvian fissure
• Borders on the insula in the depth of the sylvian fissure.

3) <u>Angular Gyrus (AG)/ BA 39:</u> In parietal lobe
• Surrounds the posterior end of the superior temporal sulcus
• follow posterior portion of the superior temporal gyrus into parietal lobe (go medial to define the depth of the posterior ascending ramus of the sylvian fissure – it has to connect)
• Bounded anteriorly by the supramarginal gyrus
• Bounded posteriorly by the parieto-occipital sulcus

4) <u>Supramarginal Gyrus (SMG)/ BA 40:</u>
• Found on either side of the ascending ramus of the sylvian fissure
• Anterior border = inferior portion of the postcentral sulcus
• Posterior border = angular gyrus
• Superior border = intraparietal sulcus

5) <u>Wernicke's + (W+):</u> Posterior third of the superior temporal gyrus and middle temporal gyrus
Superior Temporal Gyrus (BA 22):
• Anterior border = find the most anterior point of Heschl gyrus and draw a vertical line down to the superior temporal sulcus
• Posterior border = draw a vertical line from the upper inflection of the posterior ascending ramus of the sylvian fissure until the end of the superior temporal suclus
• Superior border: sylvian fissure
• Inferior border = superior temporal sulcus
Middle Temporal Gyrus (BA 21):
• Anterior border = find the most anterior point of Heschl gyrus and draw a vertical line down to the inferior temporal sulcus
• Posterior border = draw a vertical line from the upper inflection of the superior temporal suclus until the end of the inferior temporal suclus
• Superior border = superior temporal sulcus
• Inferior border = inferior temporal sulcus

LIST OF REFERENCES

Abo, M., Senoo, A., Watanabe, S., Miyano, S., Doseki, K., Sasaki, N., et al. (2004). Language-related brain function during word repetition in post-stroke aphasics. *Neuroreport, 15*(12), 1891-1894.

Barlow, T. (1877). On a case of double cerebral hemiplegia, with cerebral symmetrical lesions. *British Medical Journal, 2*, 103-104.

Basso, A., & Farabola, M. (1997). Comparison of Improvement of Aphasia in Three Patients with Lesions in Anterior, Posterior, and Antero-posterior Language Areas. *Neuropsychological Rehabilitation, 7*(3), 215-230.

Basso, A., Gardelli, M., Grassi, M. P., & Mariotti, M. (1989). The role of the right hemisphere in recovery from aphasia: Two case studies. *Cortex, 25*, 555-566.

Bihan, D. L., Mangin, J. F., Poupon, Clark, C. A., Pappata, S., Molko, N., et al. (2001). Diffusion Tensor Imaging: Concepts and Applications. *Journal of Magentic Resonance Imaging, 13*, 534–546.

Blank, S. C., Bird, H., Turkheimer, F., & Wise, R. J. (2003). Speech production after stroke: the role of the right pars opercularis. *Annals of Neurology, 54*(3), 310-320.

Borovsky, A., Saygin, A. P., Bates, E., & Dronkers, N. (2007). Lesion correlates of conversational speech production deficits. *Neuropsychologia, 45*(11), 2525-2533.

Breier, J. I., Castillo, E. M., Boake, C., Billingsley, R., Maher, L., Francisco, G., et al. (2004). Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *Neuroimage, 23*(4), 1308-1316.

Cao, Y., Vikingstad, E. M., George, K. P., Johnson, A. F., & Welch, K. M. (1999). Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke, 30*(11), 2331-2340.

Cornelissen, K., Laine, M., Tarkiainen, A., Jarvensivu, T., Martin, N., & Salmelin, R. (2003). Adult brain plasticity elicited by anomia treatment. *Journal of Cognitive Neuroscience, 15*(3), 444-461.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance images. *Computers in Biomedical Research, 29*, 162-173.

Crinion, J., & Price, C. J. (2005). Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. *Brain, 128*(Pt 12), 2858-2871.

Crinion, J. T., & Leff, A. P. (2007). Recovery and treatment of aphasia after stroke: functional imaging studies. *Current Opinion in Neurology, 20*, 667–673.

Crosson, B., McGregor, K., Gopinath, K., Conway, T., Benjamin, M., Chang, Y.-L., et al. (2007). Functional MRI of Language in Aphasia: A Review of the Literature and the Methodological Challenges. *Neuropsychology Review, 17*(2), 157-177.

Crosson, B., Moore, A. B., Gopinath, K., White, K. D., Wierenga, C. E., Gaiefsky, M. E., et al. (2005). Role of the right and left hemispheres in recovery of function during treatment of intention in aphasia. *Journal of Cognitive Neuroscience, 17*(3), 392-406.

Damasio, H. (1995). *Human brain anatomy in computerized images.* New York: Oxford University Press.

Dronkers, N. F., Wilkins, D. P., Van Valin, R. D., Jr., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition, 92*(1-2), 145-177.

Duffau, H., Bauchet, L., Lehericy, S., & Capelle, L. (2001). Functional compensation of the left dominant insula for language. *Neuroreport, 12*(10), 2159-2163.

Dunn, L. M., & Dunn, D. M. (2007). The *Peabody Picture Vocabulary Test, Fourth Edition*. Bloomington, MN: NCS Pearson, Inc.

Gold, B. T., & Kertesz, A. (2000). Right hemisphere semantic processing of visual words in an aphasic patient: an fMRI study. *Brain and Language, 73*(3), 456-465.

Goodglass, H., & Kaplan, E. (1983). *The Assessment of Aphasia and Related Disorders* (Second ed.). Philadelphia: Lea & Febiger.

Gopinath, K., Crosson, B., McGregor, K., Peck, K. K., ChangY.-L., Moore, A., Sherod, M., Cavanagh, C., Wabnitz, A., Wierenga, C., White, K., Cheshkova, S., Krishnamurthy, V., Briggs, R. W. (in press). Selective detrending method for reducing task-correlated motion artifact during speech in event-related FMRI. *Human Brain Mapping*.

Heiss, W. D., Karbe, H., Weber-Luxenburger, G., Herholz, K., Kessler, J., Pietrzyk, U., et al. (1997). Speech-induced cerebral metabolic activation reflects recovery from aphasia. J *Neurol Sci,* 145(2), 213-217.

Heiss, W. D., Kessler, J., Thiel, A., Ghaemi, M., & Karbe, H. (1999). Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. *Annals of Neurology, 45*(4), 430-438.

Heiss, W. D., & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language, 98*(1), 118-123.

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983*). The Boston Naming Test*. Philadelphia, PA: Lea & Febiger.

Karbe, H., Thiel, A., Weber-Luxenburger, G., Herholz, K., Kessler, J., & Heiss, W. D. (1998). Brain plasticity in poststroke aphasia: what is the contribution of the right hemisphere? *Brain and Language, 64*(2), 215-230.

Kertesz, A. (1982). *Western Aphasia Battery*. Orlando, FL: Grune & Stratton.

Kertesz, A., Lau, W. K., & Polk, M. (1993). The Structural Determinants of Recovery in Wernicke's Aphasia. *Brain and Language, 44*(2), 153-164.

Kertesz, A., & McCabe, P. (1977). Recovery Patterns and Prognosis in Aphasia. *Brain, 100*(1), 1-18.

Kinsborne, M. (1971). The minor cerebral hemisphere as a source of aphasic speech. *Archives of Neurology, 25,* 302-306.

Knopman, D. S., Selnes, O. A., Niccum, N., & Rubens, A. B. (1984). Recovery of naming in aphasia: Relationship to fluency, comprehension and CT findings. *Neurology, 34,* 1461-1470.

Kreisler, A., Godefroy, O., Delmaire, C., Debachy, B., Leclercq, M., Pruvo, J.-P., et al. (2000). The anatomy of aphasia revisited. *Neurology, 54*(5), 1117-1123.

Lazar, R. M., Marshall, R. S., Pile-Spellman, J., Duong, H. C., Mohr, J. P., Young, W. L., et al. (2000). Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation. *Neuropsychologia, 38,* 1325-1332.

Leger, A., Demonet, J. F., Ruff, S., Aithamon, B., Touyeras, B., Puel, M., et al. (2002). Neural substrates of spoken language rehabilitation in an aphasic patient: an fMRI study. *Neuroimage, 17*(1), 174-183.

Martin, P. I., Naeser, M. A., Theoret, H., Tormos, J. M., Nicholas, M., Kurland, J., et al. (2004). Transcranial magnetic stimulation as a complementary treatment for aphasia. *Seminars on Speech and Language, 25*(2), 181-191.

Miura, K., Nakamura, Y., Miura, F., Yamada, I., Takahashi, M., Yoshikawa, A., et al. (1999). Functional magnetic resonance imaging to word generation task in a patient with Broca's aphasia. *Journal of Neurology, 246*(10), 939-942.

Naeser, M., Palumbo, C. L., Helm-Estabrooks, N., Stiassny-Eder, D., & Martin, A. (1989). Severe nonfluency in aphasia: Role of the medial subcallosal fasciculus and other white matter pathways in recovery of spontaneous speech. *Brain, 112*(1), 1-38.

Naeser, M., Palumbo, C. L., & Stiassny-Eder, D. (1990). Late recovery of auditory comprehension in global aphasia:Improved recovery observed with subcortical temporal isthmus lesion vs. Wernicke's cortical area lesion. *Archives of Neurology, 47,* 425-432.

Naeser, M. A., Baker, E. H., Palumbo, C. L., Nicholas, M., Alexander, M. P., Samaraweera, R., et al. (1998). Lesion Site Patterns in Severe, Nonverbal Aphasia to Predict Outcome With a Computer-Assisted Treatment Program. *Archives of Neurology, 55*(11), 1438-1448.

Naeser, M., Theoret, H., Kobayashi, M., Martin, P., Nicholas, M., et al. (2002). *Modulation of cortical areas with repetitive transcranial magnetic stimulation to improve naming in nonfluent aphasia* [Abstract #133]. 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. Available on CD-ROM in Neuroimage 16(2).

Ono, M., Kubik, S., & Abernathey, C. D. (1990). *Atlas of the cerebral sulci*. New York: Thieme Medical Publishers, Inc.

Seghier, M., Lazeyras, F., Momjian, S., Annoni, J. M., de Tribolet, N., & Khateb, A. (2001). Language representation in a patient with a dominant right hemisphere: fMRI evidence for an intrahemispheric reorganisation. *Neuroreport, 12*(13), 2785-2790.

Selnes, O. A., Knopman, D. S., Niccum, N., Rubens, A. B., & Larson, D. (1983). Computed tomographic scan correlates of auditory comprehension deficits in aphasia: A prospective recovery study. *Annals of Neurology, 13*(5), 558-566.

Warburton, E., Price, C. J., Swinburn, K., & Wise, R. J. (1999). Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. *Journal of Neurology, Neurosurgery, and Psychiatry, 66*(2), 155-161.

Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Muller, S. P., Bier, D., et al. (1995). Recovery from Wernicke's Aphasia: A positron emission tomographic study. *Annals of Neurology, 37*, 723-732.

Wise, R. J. S. (2003). Language systems in normal and aphasic human subjects: functional imaging studies and inferences from animal studies. *Br Med Bull, 65*(1), 95-119.

BIOGRAPHICAL SKETCH

Zvinka Zlatar received her Bachelor of Arts degree in psychology from the University of Nevada, Las Vegas in 2005 and her Master of Science degree in psychology from the University of Florida in the spring of 2009. As a post-baccalaureate, she worked at the University of Florida's NIMH Center for the Study of Emotion and Attention and the Brain Imaging Rehabilitation & Cognition Lab. Zvinka is currently a second-year neuropsychology graduate student in the University of Florida's Clinical and Health Psychology program. Her research focuses primarily on studying cognition in old age and how the brain-behavior relationship becomes affected after stroke and degenerative disease, as well as in healthy aging.

Recently, Zvinka has been involved in an intention-based language treatment study aiming to improve language production in individuals with nonfluent aphasia. Currently, she is involved in conducting an fMRI study that will investigate brain activity and cognitive differences as a function of fitness level in sedentary and fit younger and older adults.