# FUNCTIONAL MAGNETIC RESONANCE IMAGING OF OVERT LANGUAGE PRODUCTION IN APHASIA REHABILITATION: THE CONTRIBUTION OF THE LANGUAGE NONDOMINANT HEMISPHERE

By

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To my family, whose sacrifices were freely given, whose support was constant, and to whom I am blessed to be able to give my love to everyday.

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Neural activity during language production in aphasia typically has been measured using functional magnetic resonance imaging (fMRI) during silent production tasks. There are many potential disadvantages associated with the use of silent production tasks, including an inability to separate correct versus incorrect responses. We have modified a technique used in neurologically normal subjects that allows recording and analysis of overt response generation during fMRI. Six aphasic patients completed an event-related word generation (verbal fluency) task during fMRI at two time periods. The patients completed the first fMRI scan prior to beginning an experimental language rehabilitation treatment designed to improve language production through recruitment of right hemisphere mechanisms. The second fMRI scan was completed following completion of treatment, approximately 7-10 weeks after the initial scan. A tracing technique was used to define a region of interest within the right hemisphere homologue of Broca's area in order to precisely quantify the amount of neural activity within this

discrete region of the brain. This technique allowed pretreatment and posttreatment scans to be compared to examine predicted changes in neural activity in the right hemisphere homologue of Broca's area. Results suggest that for some nonfluent aphasic patients, a positive response to language rehabilitation was associated with a reorganization of function to the right hemisphere homologue of Broca's area. Subsequently, implications for neural substrates of recovery from aphasia are discussed.

# CHAPTER 1
# INTRODUCTION

The advent of functional magnetic resonance imaging (fMRI) offers additional information about localization of brain function and provides a unique opportunity to examine the areas of the brain that are still functional following brain damage. In addition, fMRI allows a more comprehensive examination of the impact of a brain lesion and an analysis of functional perilesional areas. While language has not been the focus of the majority of fMRI studies, its role in the localization of function debate has been both profound and persistent, lasting well over a century.

## Anatomy of Language

While one of the first functions to be ascribed to a specific location, language-related functions dominated literature in the latter part of the 19$^{th}$ century, particularly due to the work of Paul Broca and Carl Wernicke. It was during this time that the "classical model" of language was developed and popularized, a model still commonly used in current research (Binder et al., 1997; Broca, 1861/1997; Lichtime, 1885). This model proposes that there are two primary locales for language: 1) Broca's area, a frontal and expressive language area for planning, speech production, and writing movements, and 2) Wernicke's area, a posterior and receptive language area for analysis and identification of the components of language (for review see Binder et al., 1997; Broca, 1861/1997; Finger, 1994/1997; Lichtime, 1885). More recent research continues to provide support for the classical model via neuroimaging by showing localized activation in the inferior frontal gyrus (IFG; Broca's area), and in the superior temporal gyrus (STG; Wernicke's area) (Binder et al., 1997; Foundas, Eure, Luevano, & Weinberger, 1998). Furthermore, additional studies have begun to add to the list of language-related functions that Broca's area appears to be responsible for, namely syntactic processing, and feedback/reanalysis (Sakai, Hashimoto, & Homae, 2001). It must also be noted, however, that although language is predominantly associated with these areas, language-related functions are not exclusively localized to these areas (Foundas et al., 1998).

Of great importance to language research are consistent findings in right-handed people that language is predominantly a left hemisphere phenomenon. The demonstrated anatomical asymmetries in frontal and temporal speech-language regions appear to consistently favor the left hemisphere across multiple measurement techniques including fMRI, magnetic resonance imaging (MRI), and positron emission tomography (PET) (Burton, Small, & Blumstein, 2000; Foundas et al., 1998; Holland et al., 2001; Musso et al., 1999). Recent research also indicates a developmental component to language lateralization, as left hemisphere specialization (noted by activation) for language appears to increase with age throughout childhood, while the amount of area activated in the right hemisphere during language tasks appears to be strongly negatively correlated with age (Holland et al., 2001). Subsequently, research literature reserves "Broca's" and "Wernicke's" areas only for the left hemisphere, while the homotopic areas in the right hemisphere are referred to as "Broca's homologue" and "Wernicke's homologue."

While not discounting the importance of Wernicke's area as the receptive language locale, the focus of many recent studies has been Broca's area, its role in speech-language production, and its right hemisphere homologue. Broca's area is comprised of two anatomical structures: pars triangularis (PTR; Brodmann's area 45) and pars opercularis (POP; Brodmann's area 44) (Crosson et al., 2001; Foundas et al., 1998; Moore, Crosson, Gockay, Leonard, & Foundas, 2000; Moore, Loftis et al., 2001). Both regions are found on the lateral extent of the left hemisphere and are defined by rami extending from the Sylvian Fissure. Specifically, according to Foundas et al. (1998), pars triangularis may be defined as "extending superiorly to the inferior frontal sulcus, inferior to the anterior horizontal ramus (AHR), and caudally to the anterior ascending ramus (AAR)." Pars opercularis is adjacent to pars triangularis, and is "bounded superiorly by the inferior frontal sulcus" and "bounded inferiorly by the anterior ascending ramus (AAR) and caudally by the precentral sulcus" (Foundas et al., 1998).

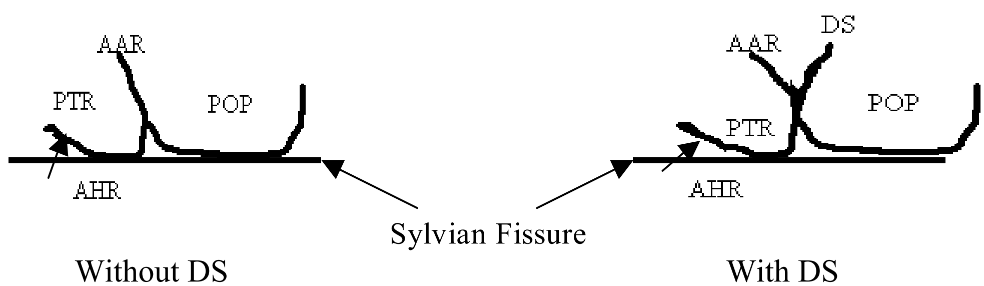


Figure 1. Anatomical landmarks for pars triangularis and pars opercularis without and with a diagnol sulcus (AHR: anterior horizontal ramus, AAR: anterior ascending ramus, DS: diagnol sulcus, PTR: pars triangularis, POP: pars opercularis).

While the lateral-frontal region, known as Broca's area, is predominantly associated with speech production, normal language production appears to involve both medial- and lateral-frontal cortices (Abdullaev & Posner, 1998; Crosson, Rao et al., 1999; Crosson, Sadek et al., 1999). It has been suggested that the intentional, or initiation, component for language is primarily localized in the medial-frontal cortex, while the production component is thought to be primarily localized in the lateral-frontal cortex (Abdullaev & Posner, 1998; Crosson, Rao et al., 1999; Crosson, Sadek, Bobholz et al., 1999; Crosson, Sadek, Maron et al., 2001). There also appears to be a temporal relationship between the two cortices, as noted by event-related potential (ERP) studies, with the medial-frontal areas being activated prior to the lateral-frontal areas (Abdullaev & Posner, 1998). In summary, it appears that normal fluent language production requires synchrony of function between left hemisphere medial- and lateral-frontal brain regions.

## Aphasia

Aphasia is an acquired disorder resulting from brain dysfunction in which one or more components of language (e.g. comprehension, production, structure, or communicative intention) are disrupted (Broca, 1861/1997; Finger, 1994/1997; Nadeau, Rothi, & Crosson, 2000). Aphasia can follow stroke and traumatic brain injury, and may also be associated with diseases affecting brain substance and function (Nadeau et al., 2000). It is a persistent and enduring condition affecting language structures in the left hemisphere (Broca, 1861/1997; Finger, 1994/1997; Nadeau et al., 2000). Incidence rates approximate stroke occurrence at 300-500 people per every 100,000, and it is the leading health care problem in the U.S. that requires rehabilitative services (Nadeau et al., 2000). Twenty-five percent of stroke patients also suffer from an associated aphasia (Nadeau et al., 2000).

Nonfluent aphasia is a particular type of aphasia that is characterized by a disruption in language production. Language tends to be halting, agrammatic, and telegraphic. One type of nonfluent aphasia is referred to as Broca's aphasia given its association with dysfunction in Broca's area. Following the localization of language production dysfunction to Broca's area, research efforts began to focus on rehabilitation and recovery of language function in nonfluent aphasics. Subsequently, debate ensued between proponents of "recovery of function" and proponents of "reorganization of function" (Cappa, 2000; Khatri & Hier, 1999; Musso et al., 1999; Rosen et al., 2000). Proponents of recovery of function believe that areas initially damaged by brain injury in the left hemisphere heal and subsequently reclaim their duties (Khatri & Hier, 1999; Rosen et al., 2000). In contrast, proponents of reorganization of function believe that the areas in the right hemisphere, homologous to the injured areas in the left hemisphere, assume the duties of the injured areas that may no longer be activated, or that may be unable to sustain activation (Cappa, 2000; Khatri & Hier, 1999; Rosen et al., 2000).

Work by Musso et al. (1999) provides evidence that the right hemisphere homologue of Wernicke's area assists in compensating for the loss of function following injury in Wernicke's area, suggesting a reorganization of receptive language to the right hemisphere following left hemisphere injury. Musso et al. (1999) further suggests that the reorganization of language to the right hemisphere, which contributes to recovery of language in aphasic patients, results from a re-coordination of a network of areas, suggesting a concerted effort of support from many areas for more proficient language recovery. However, Thomas, Altenmuller, Marckmann, Kahrs, and Dichgans (1997) measured DC-potentials in nonfluent and fluent aphasics (characterized by dysfunction in Broca's and Wernicke's areas respectively) and found that reorganization of language function depended upon the type of aphasia. Their findings suggest that nonfluent aphasics initially (2-4 weeks post injury) demonstrate a reorganization of function to the right hemisphere following injury to Broca's area, but follow-up studies (conducted when recovery was clinically evident) suggest a recovery of function, as noted by a complete shift of laterality back towards the left hemisphere (Thomas et al., 1997). However, this study also suggests that fluent aphasics demonstrated an initial (2-4 weeks post injury) reorganization of function to the right hemisphere, that was maintained at follow-up, with no evidence of a shift of laterality back towards the left hemisphere (Thomas et al., 1997). A third set of findings indicate that recovery of function by the left hemisphere, or reorganization of function to the right hemisphere, may be mediated by the severity of damage to the left hemisphere (Karbe et al., 1998). The findings presented in Karbe et al. (1998) and Belin et al. (1996) suggest an inverse correlation between the functional recovery of the traditional left hemisphere language areas, and perilesional areas, and right hemisphere reorganization. This further suggests that recovery of language production competency in the left hemisphere reduces the permanent compensatory functioning of the right hemisphere; moreover, more permanent loss of functioning in the left hemisphere suggests increased compensatory functioning in the right hemisphere (Karbe et al., 1998). In summary, previous studies suggest evidence for both recovery of function in the left hemisphere and reorganization of function to the right hemisphere, but that effort in one hemisphere appears to be inversely proportionate to functioning in the other.

## Functional Magnetic Resonance Imaging

The rationale behind the use of functional neuroimaging resides in the specific information processing demands of the brain during task performance (Fiez, 2001). As the demands of the task are met, changes in neural activity occur in areas of the brain associated with task completion (Fiez, 2001). It has been suggested that imaging methods based on blood flow are more sensitive to changes in neuronal activity than other imaging methods, such as those that use cerebral metabolism as the basis for measuring neuronal activation (e.g. PET and SPECT, Nadeau & Crosson, 1995). Consequently, functional magnetic resonance imaging (fMRI) has become a popular choice among imaging techniques. FMRI is a non-invasive technique that measures neural activity via the properties of the hydrogen atom and hemoglobin; the distribution of the magnetic signal is related to the distribution of water in the brain tissue, as well as to the amount of oxygen being carried by the hemoglobin (Fiez, 2001). When blood flow to a specific area of the brain increases to meet the demands of a task, the number of oxygen-carrying hemoglobin molecules increases; likewise, the percentage of deoxyhemoglobin (hemoglobin not carrying oxygen) in these areas decreases (Fiez, 2001; Rijntjes & Weiller, 2002). Blood oxygen level dependent (BOLD) fMRI images are created via the disruption in the strength of the hydrogen atoms' magnetic signal caused by the decrease in the percentage of deoxyhemoglobin that subsequently causes an increase in the local signal of the hydrogen atoms in the brain tissue (Fiez, 2001). Thus, fMRI images are created by the changing in blood flow to areas of the brain mediated by the changing percentages of deoxyhemoglobin in the brain tissue (Fiez, 2001). Once functional neural activity has been measured, the functional images must be correlated to anatomic images and registered in order to link the observed changes in blood flow to a specific area of the brain (Nadeau & Crosson, 1995).

Blood flow changes during fMRI are known as hemodynamic responses (Figure 2) and they accompany neuronal changes. Once a hemodynamic response is initiated (typically 2-4 seconds following trial initiation), it will typically peak 6-8 seconds after initiation and will resolve, or return to baseline levels, at 10-12 seconds after initiation (Fiez, 2001).

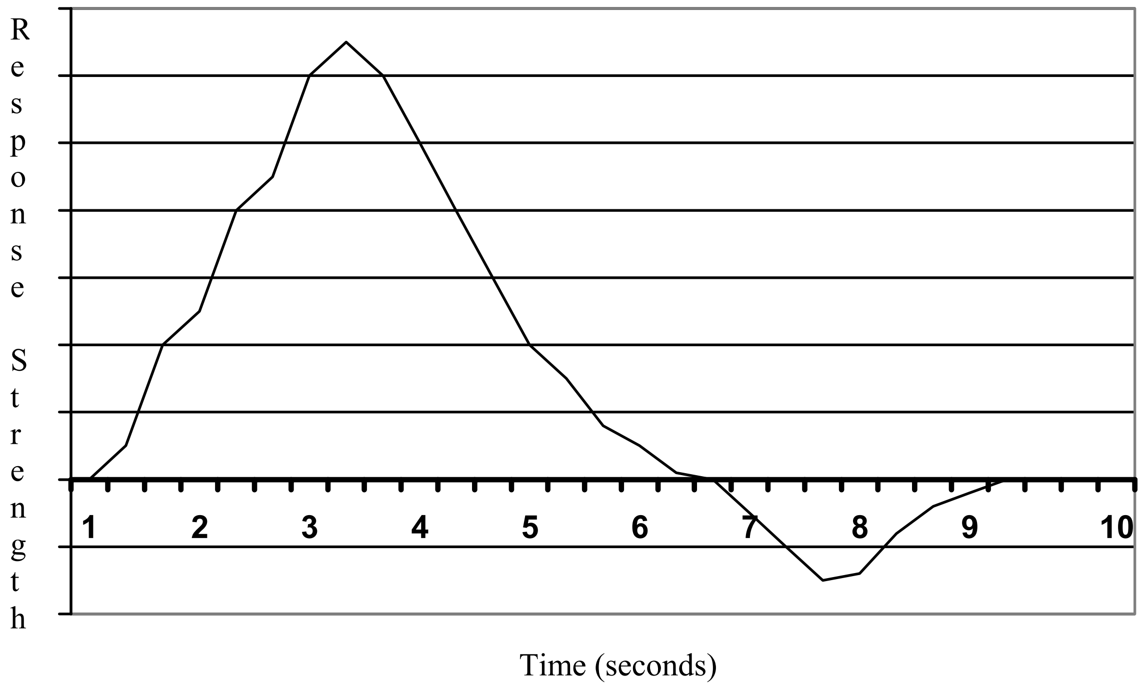


Figure 2. Example of hemodynamic response

In order to capture the hemodynamic response, two types of behavioral task designs may be used: a blocked design or an event-related design. A blocked design attempts to capture a stronger hemodynamic response by alternating between “active” blocks and “control” blocks (Fiez, 2001). “Active” blocks contain a number of stimuli with short interstimulus intervals, and “control” blocks contain several control stimuli with short interstimulus intervals, or a lengthy period of rest. The rationale for using a blocked design is to provoke multiple hemodynamic responses that will produce stronger activation because there is no time for the hemodynamic response to return back to baseline before the presentation of the next stimulus, thereby causing an additive effect in the amount of measured response. In contrast, an event-related design attempts to capture a single hemodynamic response by alternating between a single “active” stimulus and a single “control” stimulus, or rest period, separated by a lengthy interstimulus interval. The rationale for using an event-related design is so that a single hemodynamic response is initiated, peaks, and returns to baseline before the next "active" stimulus is presented. Event-related designs appear to maintain significant advantages over blocked designs due to increased flexibility in design and analysis. For example, event-related designs provide the opportunity to analyze response patterns via overt responses, examine task accuracy, and changes in behavior over time; advantages that cannot be obtained with block designed paradigms.

**FMRI and Aphasia**

The advent of fMRI marked a shift in the focus of brain injury research from an examination of which brain areas were injured, to an examination of which brain areas were still functional (Khatri & Hier, 2000). FMRI surfaced amidst the recovery of function versus reorganization of function debate. This imaging technique can answer many questions regarding recovery of function that traditional methods cannot answer. Specifically related to aphasia, fMRI may help determine whether recovery of linguistic ability following a sustained period of aphasia is attributable to a recovery of function in the left hemisphere (Khatri & Hier, 2000; Pizzamiglio, Galati, & Committeri, 2001; Rosen et al., 2000), a reorganization of function to the right hemisphere (Cappa, 2000; Khatri & Hier, 2000; Pizzamiglio et al., 2001; Rosen et al., 2000), or whether linguistic recovery results from the coordination of efforts in both hemispheres.

A number of fMRI research efforts have been pursued in attempts to end the debate between recovery of function and reorganization of function, but results indicate support for both sides depending upon various mediating factors. For example, one study found that left-sided brain damage acquired in early childhood appears to induce a significant shift of activation associated with language production to the undamaged right hemisphere (Staudt et al., 2001). Another study found that in patients with language deficits resulting from a left hemisphere infarct, there was a significant increase in the amount of activation in the right hemisphere areas homologous to the language areas of the left hemisphere, however the decrease in the amount of activation in the traditional left hemisphere language areas was not significant, but activity was shifted away from the lesion site (Cao, Vikingstad, George, Johnson, & Welch, 1999). This rearrangement of activity to other areas of the left hemisphere that were anterior and posterior to the lesion site also appeared to be associated with decreased activity in other intact regions of the left hemisphere (Cao et al., 1999). (This phenomenon of intrahemispheric rearrangement of activity to perilesional areas anatomically connected to the lesion site is known as diaschisis (Pizzamiglio et al., 2001; Rijntjes & Weiller, 2002)). In contrast, Gold and Kertesz (2000) and Rosen et al. (2000), found strong right hemisphere activation in the right inferior frontal gyrus (Broca's homologue), with little activity detected in or near the damaged left inferior frontal gyrus (Broca's area) in aphasic patients.

Previous fMRI studies with aphasic patients have also used covert, or silent, response generation to measure neural activation (Rosen et al., 2000). Few studies have used an overt, or spoken, word generation technique with fMRI in healthy subjects (de Zubicaray, Wilaon, McMahon, & Muthiah, 2001), and only one study has used this technique with nonfluent aphasic patients (Miura et al., 1999). Covert response generation methodology is problematic since there is no controlling for task adherence and completion. Thus, analyses and subsequent results may be corrupted due to subject unresponsiveness, or error, in spite of well-controlled debriefing processes. Covert language studies also assume that subvocal articulation will activate the same areas with the same intensity as overt vocalization, but findings comparing overt and covert paradigms suggest that subvocal and overt articulations evoke different hemodynamic response patterns (de Zubicaray et al., 2001; Rosen et al., 2000). Also, since speech production disruption is the essence of nonfluent aphasia, covert responding is not a true measurement of the associated neural disruption. Further, it has been reported that aphasic patients have complained that the words they think and intend to say do not necessarily correspond with what they produce (Huang, Carr, & Cao, 2001).

Previous fMRI studies with aphasic patients have used both blocked and event-related designs that have revealed noteworthy findings, but these designs have been associated with a covert response paradigm. There are many advantages to using an event-related paradigm requiring overt responses during fMRI (Burton et al., 2001; Caplan & Dapretto, 2001). Most notably is the ability to determine whether subjects are responding appropriately to the presented stimuli. It has been suggested that a deficit in intentional processes can be better distinguished by evaluating responses according to their correctness. As noted earlier, intentional processes underlie speech production by coordinating internal speech with motor movement initiations that facilitate speech production. To further assess neural activation, response based activation may be compared according to type of response (e.g., *correct* and *incorrect*). Responses may be separated and coded as *correct* and *incorrect/other* responses, thus allowing the activity levels of each response set to be measured and subsequently compared. Response times may then be calculated and activation associated with actual speech production can be measured. The reason for the dearth of studies requiring overt responses is primarily due to movement during scanning solicited by overt responding. This movement potentially introduces motion artifacts into functional scans that can corrupt the images. The present study controls for motion artifact by precisely recording the times at which participants initiate verbal responses, and excluding images affected by motion from the modeled hemodynamic response. This technique excludes the corrupted images thereby preserving the true hemodynamic responses associated with overt responding (the excluded images now become part of the error term). Thus, by using a more controlled methodology, the present study will provide a better measure of neural activity associated with language production, as measured by fMRI.

## Hypotheses

The present study proposes that if patients show significant change in language abilities following treatment, then a change in neural activation during an fMRI language production task will be observed. Specifically, these changes in neural activity will be evident in medial-frontal (e.g. pre-supplementary motor area) and lateral-frontal (e.g. Broca's area and right hemisphere homologue to Broca's area) regions. Changes in these areas are believed to be associated with improved language function. In this first analysis of these data, I will present findings from only the right hemisphere homologue of Broca's area. There are three potential manifestations of observable change: 1) an increase in functional activity from pretreatment to posttreatment scans indicative of a reorganization of function to the right hemisphere homologue of Broca's area, 2) a decrease in functional activity from pretreatment to posttreatment scans suggesting initial reorganization of function to the right hemisphere and then possible lateral shift back to the left hemisphere (further analyses of perilesional areas in the left hemisphere should be examined for a potential recovery of function by these areas), 3) no right hemisphere functional activity, or no change in right hemisphere activation suggesting that activity associated with language production did not reorganize to the right hemisphere, or that activity in the right hemisphere homologue of Broca's area was stable.

# CHAPTER 2
# METHODS

## Participants

Nine nonfluent aphasic patients (4 men, 5 women) with middle cerebral artery vascular accidents participated in this study. All participants fulfilled the following inclusion criteria: documented left hemisphere middle cerebral artery (MCA) cerebral vascular accident (CVA), demonstrated nonfluent aphasia, premorbidly right-handed, native English speaker, height and weight compatible with the scanning environment, and concurrent enrollment in the Intention treatment for nonfluent language production, explained below. Participants were excluded if they met any of the following exclusion criteria: claustrophobia, metal in the body (e.g. pins, plates, rods, screws, non-removable dental work, non-removable body piercings, shrapnel, cardiac pacemaker or other implanted device), internal birth control device, tattooed eyeliner, artificial limb/joint, metallic fixation device, premorbid diagnosis of learning disability, diagnosis of psychiatric disorder or psychiatric hospitalization, prior treatment for alcohol or drug abuse, and pregnancy or possible pregnancy. Additional exclusion criteria included unconsciousness > 5 minutes, seizures or fainting spells not associated with stroke, and neurological disorders other than stroke. Nine patients were enrolled in both the treatment and imaging components of the study. However, one patient was unable to complete the imaging component due to discomfort during scanning, and excessive movements during scanning corrupted two patients' images. Also, during data analyses, a fourth patient's pretreatment images could not be analyzed and subsequent comparisons to posttreatment images could not be made. Subsequently, pre and posttreatment comparisons could be made for only five patients (3 men, 2 women; mean age = 59.8 years, SD = 11.76 years, range 46-70 years; mean number of months post-stroke = 60.8 months, SD = 62.06 months, range = 8-160 months).

Subject one (S01) was a 46-year-old male who suffered a left middle cerebral artery stroke that affected the temporal, frontal, and parietal lobes extending into subcortical areas. S01 was enrolled in this study at 48 months post-stroke.

Subject two (S02) was a 48-year-old female who suffered a left middle cerebral artery stroke affecting the temporal, frontal and parietal lobes with some subcortical area extension. S02 was enrolled in this study 8 months post-stroke.

Subject three (S03) was a 67-year-old male who suffered a left middle cerebral artery stroke with damage to the frontal and temporal lobes, as well as insula involvement. S03 was enrolled in this study 160 months post-stroke.

Subject four (S04) was a 70-year-old male who suffered a left middle cerebral artery stroke involving the temporal lobe and possible frontal operculum involvement. In addition, the posterior half of the insula, anterior parietal lobe and lenticulostriate endzone appear to have been affected. S04 was enrolled in this study 76 months post-stroke.

Subject five (S05) was a 68-year-old female who suffered a left middle cerebral artery stroke affecting the frontal, temporal, and parietal lobes with some subcortical involvement. S05 was enrolled in this study 12 months post-stroke.

## Procedure

### Experimental Language Rehabilitation

All patients were enrolled in a language rehabilitation treatment. Although the purpose of this study is not directly related to the language treatment study, a brief explanation of the treatment study is warranted as it sets the context for the imaging study. The language treatment was designed to target the medial-frontal cortex with the goal of transferring function from left hemisphere medial cortex to the right hemisphere homologue. It has been suggested that the area of the brain primarily responsible for the intentional component of language is the left medial-frontal cortex, whereas left lateral-frontal areas are believed to be responsible for speech production. The middle cerebral artery (MCA) innervates lateral-frontal cortices, thus a left MCA infarct disrupts the normal functioning of the left lateral-frontal areas, but not the left medial-frontal regions. While left medial-frontal regions remain intact, the normal interface of the left medial-frontal and left lateral-frontal regions during language production may be disrupted as a result of a left MCA infarct. Subsequently, nonfluent aphasia is believed to result from damage to left lateral-frontal areas associated with left middle cerebral artery vascular accidents. Attempts at language production are believed to engage the intact left medial regions that then attempt to act in concert with left lateral regions. Left lateral regions, however, have been rendered dysfunctional by the stroke. It is important to note that while left lateral areas have been rendered dysfunctional by the stroke in these five patients, right medial and right lateral regions are still intact. Given this disruption in the left hemisphere, the target of the present treatment is the right medial-frontal cortex. Medial-frontal cortex was chosen as the target area based upon previous research which indicates that right hemisphere lateral regions begin to show some neural activation during language production in patients with nonfluent aphasia (Belin et al., 1996). As noted above, it has been suggested that activation of medial regions temporally precedes activation of lateral regions. Treatment included an object-naming task that was paired with a non-meaningful movement produced by the left hand. By pairing a naming task, requiring an overt response, with a left-handed gesture, it is believed that the right hemisphere medial-frontal mechanisms are more easily engaged, thus helping to stimulate the right lateral-frontal area to take up the functions of the damaged left lateral-frontal area, namely that of speech production.

The Intention treatment (described in further detail in Richards, Singletary, Rothi, Koehler, & Crosson, 2002) was divided into three phases. All three phases of treatment were designed to target right hemisphere intentional mechanisms via complex movements/gestures generated by the subject's left hand. Progression from phase one to phase two, and then to phase three, is marked by transition from an internally generated movement prompted by external cues (e.g. a tone and flashing star), to an uncued, self-initiated complex movement sequence. By using a progressive two-cue to no-cue approach, the subject may gradually learn to pair a movement sequence with the initiation of language. The final movement/gestural sequence is a meaningless circular gesture. This gesture is both internally generated and generalizable to interactions outside of treatment. The movement sequence is neither word-related, nor symbolic in nature. The same circular gesture is used for every word and is believed to be unrepresentative of any action familiar to the subject. Treatment was conducted individually for each patient across all phases.

Phase one (10 sessions): Each subject was seated at a desk directly facing a computer monitor with their head and body facing straight ahead. To begin the trial, the therapist pressed a mouse button. A one-inch by one-inch star subsequently appeared at the center of the computer screen and a 1000 Hz tone sounded. To initiate the presence of the line drawing, each subject was instructed to lift the lid on a small box located to his/her left with their left hand and was further instructed to press a button located within the box. The button press caused the tone and star to disappear. After a two-second delay, a black-and-white drawing appeared at the center of the computer screen and a timer was initiated. If the subject named the picture correctly, the therapist pressed the mouse button that terminated the trial, stopped the timer, and the line drawing was removed from the screen. If the subject provided an incorrect response to the drawing, the therapist provided the correct name for the picture while simultaneously making the circular gesture described above with his/her left hand. The subject was instructed to repeat the corrected picture name aloud while also making the same circular gesture. This process was repeated for each of the 50 drawings, and the same 50 drawings were used for each session during this phase of treatment.

Phase two (10 sessions): The same subject positioning and treatment procedure were used in phase two as were used in phase one, except that the tone was eliminated from this phase, and a different set of 50 line drawings (not used in phase one), were depicted. Incorrect responses were corrected using the same procedure described above in phase one.

Phase three (10 sessions): The same subject positioning and treatment procedure used in phases one and two were used in phase three. The trial was initiated the same way it was initiated in phases one and two, however the subject was instructed to perform the same meaningless circular gesture performed in the previous phases with his/her left hand prior to the presentation of the line drawings. Response instructions, and correction of incorrect responses, were the same as described above in phases one and two. Fifty line drawings different from those presented in phases one and two, were used in phase three.

Two sets of line drawings were used: one set for patients receiving the balanced treatment (both high and low frequency words), and one set for patients receiving the low frequency treatment. The balanced set of line drawings contained 15 high frequency words (21-717 occurrences per million), 15 medium frequency words (4-20 occurrences per million), and 20 low frequency words (0-30 occurrences per million), in order to provide a balanced set of words and prevent subjects from obtaining ceiling effects during treatment. The low frequency set of line drawings contained 50 low frequency words. Frequencies were based on Francis and Kucera's "Frequency Analysis of the English Language" (Francis & Kucera, 1982).

**Imaging Procedure**

Prior to beginning language treatment, patients completed a baseline, or pretreatment scan. Within two weeks of completion of the treatment, patients completed a posttreatment scan. All images were acquired on a 3 Tesla GE Signa scanner using a dome-shaped RF quadrature head coil (MRI Devices). Functional imaging parameters were as follows: single shot spiral scan, gradient echo pulse sequence, TE = 18ms, TR = 1660ms, FA = 60 degrees, FOV = 200mm, matrix = 64 x 64, 32 slices with whole brain coverage, and slice thickness = 4.0mm. Structural imaging parameters were as follows: 3D spoiled GRASS sequence, TE = 6ms, TR = 23ms, FOV = 240mm, matrix size = 256 x 192 and slice thickness = 1.3mm.

A modified verbal fluency task was used in an event-related paradigm. The task used in the present study was modeled after the word generation task used in Crosson, Sadek, Maron et al., (2001). Prior to their placement in the magnet, participants provided written informed consent. The functional task was then explained and demonstrated for each participant. The participant was informed that they would be listening to a compact disc (CD) over a set of headphones while they were in the scanner. Participants were instructed to listen to the CD for a category, and to produce one exemplar of a member of that category. For example, if participants heard the category "farm animals," they might respond with "cow." Following their response, they were instructed to relax and await the presentation of the next category. Participants were instructed to give only one response for each category and were reminded to stay still in the scanner to minimize motion artifact. Participants were instructed to respond with "no" if they were unable to hear a category, unable to understand the name of the category, or if they were unable to produce a response after attempting initiation, in order to avoid coding a response as "incorrect/other" when stimuli were not audible or were uninterpretable.

FMRI stimuli were presented to subjects via a magnacoustic digital audio system and non-magnetic headset with microphone. Sound attenuation processes were performed prior to the functional scans to ensure that participants could hear the stimuli. Five runs with nine active events and variable rest intervals were used. Interstimulus intervals (ISIs) equal to 21.58 seconds, 23.24 seconds, 24.9 seconds, and 26.56 seconds were randomized throughout each run. Prior to their participation in the fMRI task, response latencies for language production were measured for each patient. Interstimulus intervals were determined using patients' mean response times plus 1.2 standard deviations, thus allowing the patients to respond to stimuli according to their own level of language production ability. Variable rest lengths between category presentations allowed time for both the participant's response, and time for the hemodynamic response to return to baseline level. Overt responses were recorded to a laptop computer via the magnacoustic microphone. The same stimuli were presented to all participants, and runs were counterbalanced across subjects and across pretreatment and posttreatment scan type for each participant. Following the fMRI procedure, participants were debriefed and offered an opportunity to view anatomical scans of their brain. At the conclusion of their pretreatment scans, participants were asked to return after completing the Intention treatment, which was typically four weeks in duration. The procedure for the posttreatment scan was identical to the procedure for the pretreatment scan. The same stimuli presented during the pretreatment scan were presented during the posttreatment scan in a randomized order.

**Imaging Analyses**

A commercial software package (Cool Edit 2000™) was used to record patient responses directly to a laptop computer. Scanner noise was also recorded during the recording of the patients' responses. The commercial software package was used to reduce the amount of scanner noise in the recorded responses so that patient responses could be heard. Patient responses were then coded off-line as *correct* or *incorrect*. Recorded responses were also analyzed to determine the time at which the response was initiated. By determining the time at which the response was initiated, the image acquisition number for each response may be determined.

Imaging data were analyzed using AFNI (3dDeconvolve) to derive functional maps based on response type. A thresholding procedure was used to minimize large vessel effects by setting voxels in which the standard deviation of the acquired time series exceeded 5% of the mean signal, to zero. Smoothing of the images was not performed. Deconvolution analyses were conducted on the *correct* responses. Since speech-related movements greatly impact the integrity of the images, the first two images after response initiation were not modeled in the subject's hemodynamic response.

Regions of interest, specifically the right hemisphere homologue of Broca's area and its components: pars triangularis homologue and pars opercularis homologue, were traced using Localization of Functional Activity (LOFA) software. The tracing techniques, based on those of Foundas et al. (1998) noted above (see Figure 1) and described in Moore, Loftis et al. (2001), were employed since the anatomical landmarks for Broca's area, specifically pars triangularis (PTr) and pars opercularis (POp), and the right hemisphere homologues of these areas, are considerably similar. For each subject, functional and anatomic images were converted to 1 $mm^3$ voxels and deformed into atlas space (Talairach & Tournoux, 1988) to normalize each brain to a standard size and orientation. The deformation process uses 10 landmark points to fit brains to atlas space. These points include: the midline posterior, superior margin of the anterior commisure (AC); the inferior margin of the posterior commisure (PC); two mid-sagittal points in the interhemispheric fissure; the left-most and right-most points in the brain; the superior-most and inferior-most points in the brain; and the anterior and posterior-most points in the brain.

The PTr and POp homologues were defined by an operator (M.E.G.) using LOFA. The operator used a cursor and the mouse to draw the homologues of the PTr and POp (which comprise Broca's homologue), and when present, the diagnol sulcus (DS). The PTr homologue was identified by finding and tracing the AHR and AAR. Tracings of the AHR were not initiated until a clearly defined ventral/rostral border was apparent. The AHR was traced from the rostral border to the intersection with the inferior portion of the AAR. The tracing was continued to include the AAR, which is the rostral boundary for the homologue of POp. Tracings for the homologue of POp followed the extent of the Sylvian Fissure from the AAR to the caudal boundary of the POp homologue, the anterior subcentral sulcus. Contiguous tracings included the DS when present. The rami for the homologues of PTr and POp were traced together on 6 to 10 contiguous sagittal slices. Within subjects, the same number of pretreatment and posttreatment images were traced. Once the homologues of PTr and POp were traced, tracings were "thickened" to 3 mm on either side of the sulci to capture the sulcal banks, and merged with *correct* response functional data to capture only activity within the region of interest. Contiguous activation clusters with a product moment correlation of 0.40 or greater and a total volume of 25 μl or greater were identified in the homologues of PTr and POp, and in the DS when present.

Many different techniques have been used to evaluate the results of fMRI. However, no standardized way of quantifying, and subsequently qualifying, functional activity has been developed. One of the most seemingly controversial facets involved in the quantification of activity involves grouping images. By collapsing across subjects, activated voxels and activity clusters may be more easily localized and evaluated.

However, when working with patients who have sustained structural brain damage, it is essential that each patient be evaluated individually. As illustrated in Figure 3, the anatomy of each brain is substantially different, suggesting that collapsing data across patients disregards important individual differences such as lesion size and location, and corrupts the investigation and understanding of which structures may still be functional in individual subjects, as some structures may have sustained more damage in some subjects than in others. Consequently, data obtained for each subject were analyzed using within-subject comparisons.

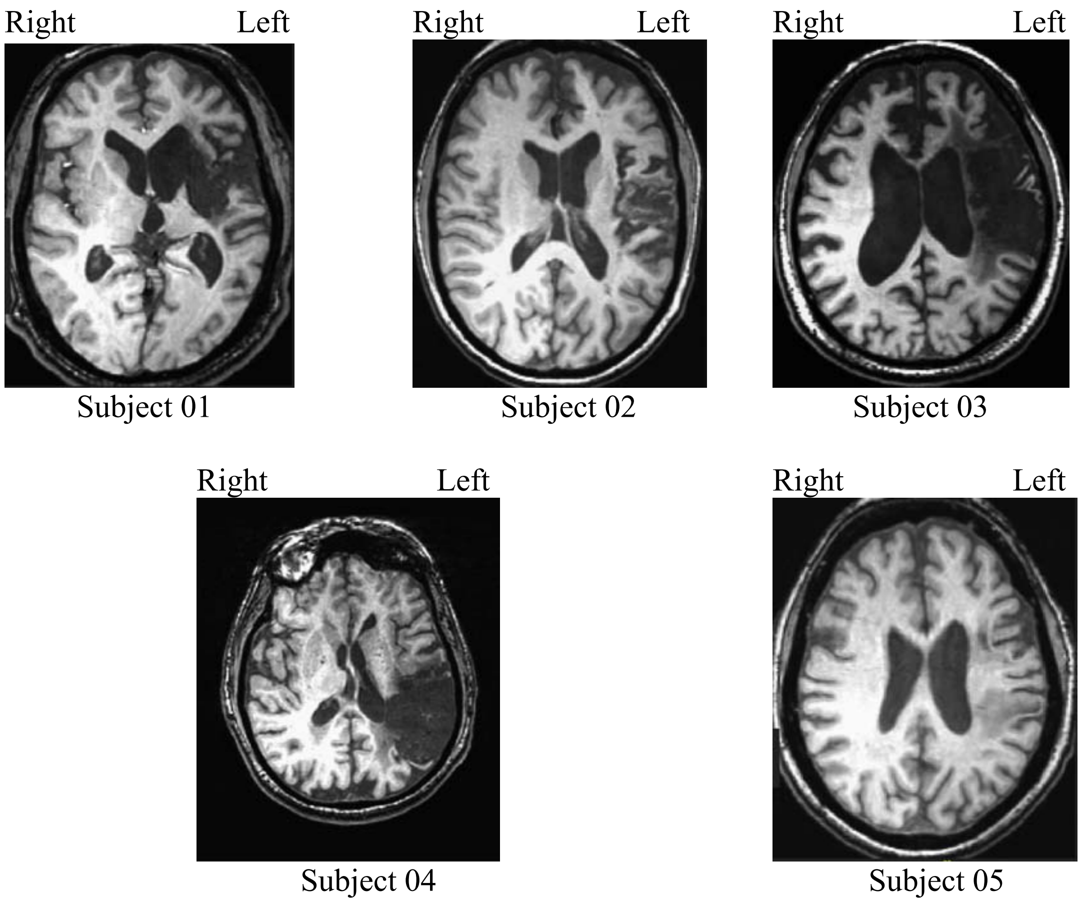


Figure 3. Axial anatomic slices illustrating individual lesions for each subject

Cluster analyses were performed on activity, captured by the merged tracings and *correct* response function, on each set of participant's images at each time period.

Conservative parameters were used to distinguish activity believed to be associated with language production. Only activated voxels with an $R^2 \geq .16$ were captured for analysis. Resulting cluster volumes for pretreatment and posttreatment activation in the region of interest were compared within subjects using chi-square analyses.

CHAPTER 3
RESULTS

Raw time series data were deconvolved with verbal response initiation input vectors, specifically *correct* response input vectors. Anatomical tracings of the homologues of PTr and POp were executed according to rules described previously in order to quantify changes in activity within the region of interest. Cluster analyses were then performed on the resulting areas of activation within the region of interest in order to determine the number of active voxels. Chi square analyses were performed on raw number of active voxels within the region of interest for each subject, in order to evaluate change in functional activity from pretreatment to posttreatment. Results are depicted in Table 1 and are summarized below.

Table 1
Functional Activity and Correct Responses for Pre- and Posttreatment Scans

| Subject | Pre treatment activity (%) | Post treatment activity (%) | $\chi^2$ | Yates' correction | Number of pre treatment correct responses | Number of post treatment correct responses |
|---|---|---|---|---|---|---|
| **1** | **1.69** | **4.91** | **74.79*** | **73.82*** | **24/45** | **32/45** |
| **2** | **0.00** | **2.25** | **98.82*** | **96.82*** | **42/45** | **44/45** |
| 3 | 0.00 | 0.00 | 0.00 | N/A | 16/45 | 16/45 |
| **4** | **2.03** | **3.90** | **16.28*** | **15.67*** | **9/18** | **9/18** |
| **5** | **43.40** | **13.24** | **304.08*** | **302.78*** | **12/18** | **12/18** |

Note: * indicates $p \leq 0.001$; **bold** indicates treatment responder

Individual subject performance during treatment was scored and evaluated by an independent, blind rater (a doctoral level speech-pathologist). The independent rater evaluated subject performance at each phase of treatment and rated each performance as showing a "positive treatment effect," "a negative treatment effect," or "no effect."

Ratings were used to further classify subjects as either a "treatment responder," or a "treatment non-responder" based on their treatment performance ratings. The C-Statistic was employed as a second method of examining response to treatment. The table below summarizes these results (Table 2).

Table 2
Independent Rater and C-Statistic Determinations of Stable Baseline and Positive Treatment Response

| Subject | Stable Baseline | | Treatment Responder | |
|---|---|---|---|---|
| | Independent Rater | C-Statistic | Independent Rater | C-Statistic |
| S01 | X | X | X | X |
| S02 | X | X | X | X |
| S03 | X | | | X |
| S04 | | X | X | X |
| S05 | X | X | X | X |

S01's performance was rated as showing a stable baseline and positive treatment effects at each phase. Subsequently, S01 was classified as a "treatment responder." S01 also showed significantly more functional activation in the right hemisphere homologue of Broca's area following treatment ($\chi^2 = 74.79$, $\underline{p} \leq 0.001$; Yates' correction = 73.82, Yates' $\underline{p} \leq 0.001$). S02's performance was rated as showing a stable baseline and positive treatment effects at each phase. S02 was classified as a "treatment responder." Furthermore, S02 showed significantly more activation in right Broca's area homologue at posttreatment when compared to pretreatment activity ($\chi^2 = 98.82$, $\underline{p} \leq 0.001$; Yates' correction = 96.82, Yates' $\underline{p} < 0.001$). S03's data indicated a stable baseline, and positive treatment effects for the first two phases of treatment, however, phase three performance was rated as "a questionable positive treatment effect," suggested by a decrease in the performance arc from phase two. This subject's performance suggests that a positive treatment effect was initially observed, but that treatment effects were not consistently maintained. Subsequently, this subject could not be classified as either a "treatment responder" or a "treatment non-responder" by the independent rater. Moreover, S03 did not show a significant change in functional activity in the right hemisphere homologue of Broca's area from pretreatment to posttreatment ($\chi^2 = 0.000087$, $p \geq .05$). S04's performance indicated an unstable baseline and no treatment effect for phase one. However, positive treatment effects were indicated in phase two and phase three performances. Subsequently, this subject was classified as a "treatment responder." S04 also showed a significant increase in the amount of functional activation in right Broca's homologue at posttreatment when compared to the pretreatment scan ($\chi^2 = 16.28$, $p \leq 0.001$; Yates' correction = 15.67, Yates' $p < 0.001$). S05's performance suggested a stable baseline, but no positive treatment effect for phase one. However, phases two and three were rated as showing positive treatment effects. Thus, S05 was also classified as a "treatment responder." An examination of functional data revealed a significant decrease in right Broca's area from pretreatment to posttreatment ($\chi^2 = 304.08$, $p \leq 0.001$; Yates' correction = 302.78, Yates' $p \leq 0.001$). In summary, four subjects were classified as treatment responders, and of those, three showed a significant increase in right hemisphere activity in Broca's homologue, while one subject showed a significant decrease in activity, and another unclassifiable subject, showed no change in the amount of activity in this area (Table 3).

Table 3
Summary of Patterns in Functional Activation from Pre- to Posttreatment

| Increased Activation in Broca's homologue | Decreased Activation in Broca's homologue | No Change in Activation in Broca's Homologue |
|---|---|---|
| S01 | | |
| S02 | S05 | S03 |
| S04 | | |

# CHAPTER 4
# DISCUSSION

An event-related word generation task requiring overt responses during fMRI was used to examine functional activity associated with language production in five patients with nonfluent aphasia resulting from left MCA stroke. Patients were instructed to provide one exemplar of a member of a category presented to them auditorally during scanning. Overt responses were coded as *correct* and *incorrect*, based on response appropriateness for each presented category. Subsequently, time of *correct* response initiation was noted for each response and the image acquisition number associated with the response was determined. *Correct* response input vectors were deconvolved with raw time series data. Anatomical tracings of the region of interest (ROI) were performed and merged with the deconvolved data, and cluster analyses were performed to determine the raw number of active voxels captured within the ROI analysis. The same procedure was used for both pre and posttreatment scans. Following the pretreatment scan, participants completed the Intention treatment designed to target right medial-frontal cortex in order to engage the intentional component of the traditionally language non-dominant hemisphere. By engaging the right medial-frontal cortex, the treatment was designed to align medial and lateral cortical activation for language production within one hemisphere. It was proposed that significant changes in language abilities following treatment would be represented by changes in measured functional activation in the right lateral-frontal region (Broca's homologue) from pre to posttreatment scans.

## Increased Right Hemisphere Activity from Pre- to Posttreatment

Findings suggest that those patients whose performance reflected positive treatment effects at each phase of treatment (S01 and S02) also showed a concurrent increase in functional activity in the right hemisphere homologue of Broca's area during an fMRI word generation task. S04, who initially showed no treatment effect at phase one of the treatment, appeared to respond positively to treatment at phases two and three. Imaging data for S04 also showed a significant increase in functional activity in Broca's homologue following treatment. These findings suggest that the rehabilitative language intervention appears to have successfully engaged right hemisphere regions for language production. Of note, lesion locus and extent is similar among these three subjects. Specifically, there is extensive frontal, temporal, and parietal damage with extensions into subcortical structures.

## Decreased Right Hemisphere Activity from Pre- to Posttreatment

One subject (S05), who initially showed no treatment effect at phase one of the treatment, appeared to respond positively to treatment at phases two and three. In contrast to the aforementioned treatment responders, imaging data for S05 revealed a significant decrease in functional activity in Broca's homologue following treatment. These findings are difficult to interpret, but not impossible. While they performed similarly in treatment, S04 and S05 differed considerably in both stroke severity and extent of damage (see Figure 3 above). S05 also differed considerably from S01 and S02 in stroke severity and extent of damage (also notable in Figure 3). Specifically, S05 sustained less extensive damage from the stroke. While subcortical structures were largely compromised in S01, S02, and S04, these structures appear relatively intact in S05. It is also possible that S05 experienced preservation of peri-lesional cortex that may not have been preserved in the other four subjects. Thus, it is possible that while a reorganization of function to the right hemisphere homologue of Broca's area was observed in the three subjects discussed above, a recovery of function may have occurred for S05 suggesting that left hemisphere functioning was restored. Further examination of the left lateral-frontal areas is required in order to more clearly understand whether a recovery of function by left lateral perilesional areas has occurred before further conclusions can be made for this subject.

### No Change in Right Hemisphere Activity from Pre- to Posttreatment

Findings also indicated that for one subject (S03), who showed variable treatment effects across time, no significant change in right hemisphere activity was observed in Broca's homologue. While no substantial conclusions can be made based on a single subject's performance, it appears that inconsistent treatment effects may be associated with no significant changes in activation in the region of interest in the right hemisphere. Further examination of S03's pre and posttreatment functional activity, particularly in the right medial areas, is warranted to examine whether treatment effects were evident in this area since it was the target area for treatment.

## Conclusions

This study documents successful implementation of a behavioral paradigm employing overt responses with aphasic patients. Use of overt responses during an fMRI behavioral paradigm offers valuable insight into activation associated with language production by allowing examination of response type and verification of task compliance. In addition, region of interest analyses may also provide valuable information that may help to determine which areas are still functional in patients who have suffered brain dysfunction. This study also suggests that fMRI provides valuable information about areas of function that may potentially influence rehabilitative efforts. Of particular importance are results from this study that suggest that the location and extent of the lesion is an important factor in language rehabilitation, specifically in terms of implications for a reorganization of function to the homologous right hemisphere regions.

## Limitations

It is important to note that while fMRI may offer further insights as to the location of activation following language rehabilitation, functional imaging is, for the moment, unable to distinguish between activity in a lesion due to incomplete infarction and activity due to new neurons and connections (Rijntjes & Weiller, 2002). Cao et al. (1999) also described difficulties in distinguishing between the unknown properties associated with the reorganization of function to the right hemisphere, namely whether a reactivation of preexisting right hemisphere mechanisms occurs, and/or determining whether a recruitment of new language areas occurs. It has been suggested that a reorganization of function to the right hemisphere is more consistent with the hypothesis that a reactivation of a preexisting language network area occurs to compensate for left hemispheric dysfunction (Cao et al., 1999; Rosen et al., 2000).

## Implications and Future Directions

It appears that the innovative techniques developed in association with this study, such as: requiring overt responses from nonfluent aphasic patients during fMRI, deconvolving imaging data based on response type (e.g. *correct* response input vectors), and excluding the first two motion affected images associated with participant response initiation from the modeled hemodynamic response; in congruence with an innovative approach to treatment and language rehabilitation, provide an appropriate measure of language production in an aphasic population.

In addition to measurement innovation, the findings from this study suggest that lesion location and extent impacts neural substrates of rehabilitation. Chronic aphasic patients with larger and more extensive left hemisphere damage, who show poorer recovery, do not appear to show spontaneous reorganization of function to the right hemisphere. However, the results of this study suggest that chronic aphasic patients with large lesions, who have poor recovery of function by the left hemisphere areas, but who respond to a treatment targeting the right hemisphere medial-frontal areas, appear to show good reorganization of function to the right hemisphere. Finally, the results of this study also suggest that chronic aphasic patients with less severe and less extensive lesions, who show good recovery in response to similar types of treatment, may initially reorganize function to the right hemisphere, but may then recover function in left hemisphere peri-lesional areas. Further investigation of left hemisphere peri-lesional areas is necessary before any substantial conclusions can be made about recovery of function in left hemisphere peri-lesional areas in less severe left MCA stroke patients. In summary, findings from this study suggest that support can be found for both the recovery of function and reorganization of function positions. Data to support these positions may be examining two different samples of patients, with studies documenting recovery of function enrolling aphasic patients with less severe and less extensive left hemisphere lesions, and studies documenting reorganization of function enrolling aphasic patients with more severe and more extensive left hemisphere lesions.

Future directions driven by the findings from this study will pursue further region of interest analyses focusing on activity in the left lateral-frontal peri-lesional areas, as well as on activity in bilateral medial-frontal regions. Analyses of left lateral-frontal peri-lesional areas may offer further insight into lesion size association with recovery of function and/or reorganization of function. Analyses of the bilateral medial-frontal regions may offer further explanation of functional activity that is more closely associated with the targeted areas of treatment and may provide a more pure measure of treatment effects associated with the Intention treatment.

The implications of measuring functional activity associated with rehabilitation are also of great importance, specifically in regard to predicting treatment effectiveness for individual patients. This research may help direct rehabilitative efforts on a patient-by-patient basis by examining lesion size and patterns of functional activation prior to treatment. This approach to treatment may better aid in developing patient-specific treatments that will most utilize areas that are still functional in each patient, thereby maximizing treatment effectiveness and maintaining subsequent recovery.

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# BIOGRAPHICAL SKETCH

Megan Elizabeth Gaiefsky was born in La Mirada, California on July 6, 1978. She graduated from Alta Loma High School in 1996 and received her Bachelor of Arts degree in psychology from Trinity University, San Antonio, Texas, in May 2000. From May 2000 through September 2000, Megan Gaiefsky was employed as a research associate in the Department of Neurology at Harbor-UCLA Medical Center Research and Education Institute in Torrance, California. In September 2000, she was asked to pursue a research assistant position in the Medical Department at Brookhaven National Laboratory in Upton, New York. She was employed in the Medical Department at Brookhaven National Laboratory from September 2000 through July 2001. In August 2001, Megan Gaiefsky enrolled in the doctoral program in the Department of Clinical and Health Psychology at the University of Florida. Her clinical and research interests are in the area of clinical neuropsychology.