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CEREBRAL PERFUSION AND DIFFUSION IN STROKE: ASSOCIATION WITH APHASIA SEVERITY IN THE EARLY PHASES OF RECOVERY

By

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A Dissertation Submitted to the Faculty of the

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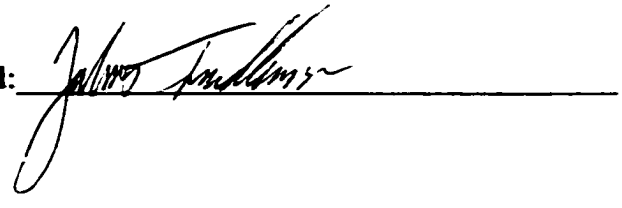
Signed: 

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ABSTRACT

The purpose of this study was to investigate the relationship between cerebral perfusion, diffusion, and aphasia severity in stroke. Nine subjects with acute ischemic stroke were examined within 24 hours of symptom onset and six were reexamined at one-month post-stroke. Examination included aphasia testing, testing of face discrimination ability, administration of the National Institutes of Health Stroke Scale, and perfusion MRI (PI), diffusion MRI (DWI), and T2-weighted MRI (T2-MRI). Subjects with a variety of aphasia types and severity participated in the study. MR images were visually inspected to verify perfusion and diffusion abnormalities. Perfusion abnormality was quantified by calculating a perfusion signal ratio of the affected hemisphere over the whole image (left/whole = ratio). Lesion volume was calculated from the DWI and T2-MRI. A visual inspection of the MR images suggested that perfusion abnormality was larger than the DWI lesion in 8 of 9 subjects. Minimal lesions were observed on DWI in three of the subjects while their PI revealed significant perfusion abnormality. The correlation (Spearman) between aphasia severity and hypoperfusion was significant in the acute stage and again at one-month post-stroke. Five of six subjects that were reexamined at one-month post-stroke experienced significant aphasia recovery. Visual inspection of their PI scans suggests that aphasia recovery was accompanied by increase in cerebral perfusion. The correlation between aphasia severity and lesion size was not statistically significant in the acute stage or at one-month post-stroke. Consequently, it is probable that cerebral hypoperfusion is a better predictor of aphasia severity and recovery in early stroke than lesion volume seen on DWI and T2-MRI.

CHAPTER I - INTRODUCTION

Recently, there has been growing interest in the relationship between neurological status, hypoperfusion, and lesion size in acute stroke patients. It is not clear how these factors may be related to aphasia severity in the acute stage. The purpose of this study was to investigate the association between aphasia severity, hypoperfusion, and lesion size following acute stroke. Below is an account of why it is important to investigate this relationship, how it was investigated in this study, followed by a description of the results, and finally, a discussion of the findings.

Background

Acute aphasia following stroke is a dynamic condition whose course is difficult to predict. Several factors are probably influential in recovery from aphasia, but a strong predictor model has not been conceptualized. One of these factors may pertain to changes in cerebral hemodynamics. That is, brain perfusion changes following stroke may play a role in the extent and timing of aphasia recovery. While many studies have explored the relationship between global neurological deficits and changes in perfusion (Barber, et al., 1998; Beaulieu, et al., 1999; Chalela, et al., 2000; Neumann-Haefelin, et al., 2000; Tong, et al., 1998), less is known about how these changes may affect the course of spontaneous recovery, or lack of it, in aphasia.

Spontaneous Recovery from Aphasia

Most patients improve following the onset of stroke compared to acute status, even without rehabilitation. This phenomenon is usually referred to as spontaneous recovery. As a result of spontaneous and/or treatment induced recovery, initial aphasia symptoms may change quite rapidly in the first days, weeks, and even months following aphasia onset. For example, a patient's language profile may change from non-fluent to fluent in a matter of days (Holland, et al., 1985). This evolution is often so fast that aphasia classification during this time may in most cases be impractical (Kertesz & McCabe, 1977; Schuell, 1954).

Rapid spontaneous recovery often makes it difficult for speech-language pathologists to assess aphasia severity as well as to set treatment goals in the acute-care setting. Weisenburg and McBride (1935) were among the first to point out this dilemma and noted that spontaneous recovery following onset of aphasia could go on for months after onset. They suggested that detailed analyses of spontaneous recovery were needed before it was possible to determine the effect of aphasia treatment. Otherwise, it is often difficult to distinguish between spontaneous and treatment induced recovery.

It is unclear what factors play a role in spontaneous recovery from aphasia. Given biographic variability as well as the extent and etiology of brain damage, it is probable that the influence of these factors on recovery from aphasia may vary significantly from one person to another. As will be discussed later,

some factors that are thought to be related to recovery have been studied more extensively than others. Increased understanding of these factors and how they relate to one another will result in better prediction of the extent and timing of spontaneous recovery from aphasia.

The number one cause of aphasia in the United States is stroke. Consequently, the study of aphasia recovery goes hand-in-hand with the study of stroke recovery. Behind heart disease and cancer, stroke is the third leading cause of death in the United States. More importantly, it is the leading cause of disabilities (language, cognitive, and physical), affecting over 600,000 Americans per year (American Stroke Association, 2000). It is not clear how many of these strokes result in aphasia. Aphasia can be a transient condition and not all patients who are aphasic in the acute stage following stroke will experience persistent aphasia. The extent and timing of recovery from aphasia have been studied intermittently over the past century and some general patterns have been identified, and are described below.

Evolution of Aphasia Following Stroke

The bulk of spontaneous recovery is thought to occur within the first two months following the onset of aphasia (Holland, 1989). This period may last longer for some patients and could extend as far as six months or even one-year post stroke (Holland, Greenhouse, Fromm, Swindell, 1989; Kertesz & McCabe, 1977; Pashek & Holland, 1988). Sarno and Levita (1971) suggested that

compared to patients with other forms of aphasia, patients with global aphasia often did not start the spontaneous recovery process until six to twelve months post-onset. In a longitudinal study of patients with stroke induced aphasia, Pedersen, Jorgensen, Nakayama, Raaschou, and Olsen (1995) found the length of the recovery period to be influenced by initial aphasia severity. They reported that patients with mild, moderate, and severe aphasia did not appear to be experiencing significant spontaneous recovery after two, six, and ten weeks, respectively. Even though different persons with aphasia may experience different extent of spontaneous recovery, it seems clear that "... the shape of the spontaneous recovery curve is negatively accelerated, with the greatest amount of improvement seen soon after stroke, and with diminishing effects progressively discernible over time." (Holland, 1989, p. 83). The recovery curve shows individual variation as a result of a number of factors related to a given patient's particular stroke. Several studies have looked at how these factors may be related to recovery from aphasia with somewhat contrasting results, as illustrated below.

Factors Related to Recovery From Aphasia

Most studies divide possible factors related to recovery from aphasia into two groups – biographical (e.g., age, gender, handedness, and premorbid abilities) and neurological (e.g., etiology of brain damage, extent and site of lesion, initial aphasia severity) (Basso, 1992; Holland, 1989). It is important to note that studies of recovery in aphasia have reported conflicting results regarding the significance

of each of these factors. Differences in study designs make it difficult to compare the outcome of one study to another. For instance, the time period for patient examination is seldom the same and criteria for patient selection vary.

Biographical factors.

Several studies have reported that aging has an adverse effect on spontaneous recovery in aphasia (Gloning, Trappi, Heiss, & Quatember, 1976; Holland, et al., 1989; Marshall, Tompkins, & Phillips, 1982). However, this finding is not supported by others (Basso, Capitani, & Vignolo, 1979; Kertesz & McCabe, 1977; Messerli, et al., 1976). It is possible that age may interact with other recovery related variables, further complicating the recovery picture. For example, overall health may have an effect on the extent of recovery giving an edge to younger patients who, in general, may be better physically prepared to endure the rigor of stroke and recovery from it. The interaction between neurological factors and age may also be a confounding variable here as it relates to recovery. For example, it is not known how the presence of dementia may affect the relationship between age and aphasia recovery (Lopez, et al., in press(a), Lopez, et al., in press(b)) or how recovery of language processing can be masked by impairments of other cognitive processes (Basso, 1992).

Contradictory results have also been reported on the relationship between gender, handedness, premorbid intelligence, and aphasia (Cherney & Robey,

2001). In short, there has been little agreement concerning the influence of any of these factors or their combination on spontaneous recovery in aphasia.

Neurological factors.

When neurological factors are considered, greater consistency emerges from the data. Patients who experience intracerebral hemorrhage are thought to begin the recovery process later than patients with ischemic stroke, and probably experience a greater restitution of function (Rubens, 1977). If patients survive intracerebral hemorrhage, then better prognosis for these survivors may be the result of displacement of nerve fibers rather than their destruction (Holland, 1989). As edema lessens during the post-stroke phase, the pressure on these fibers may decrease resulting in return of neural function (Basso, 1992).

Size of lesion is thought to be related to spontaneous recovery. Patients with larger lesions typically experience less return of function and have a lower chance of complete resolve of aphasia (Ferro, 1992; Goldenberg & Spatt, 1994). Others have suggested that lesion size within cortical areas traditionally thought to be involved in language processing is a better predictor of aphasia severity and recovery than total lesion size (Naeser, et al., 1990; Kertesz, Lau, Polk, 1993). Initial severity of aphasia has been found to be a significant predictor of spontaneous language restitution. Patients who initially have severe aphasia also have a lower probability of complete recovery from it than do patients with

initially mild or moderate aphasia (Gloning, et al., 1976; Kertesz & McCabe, 1977; Basso, et al., 1979. Holland et al., 1989.).

Most of the patients in the studies described above experienced aphasia following stroke. Other neurovascular incidents that can cause aphasia are brain tumors and traumatic brain injury. Investigations of how the brain recovers from stroke may further enlighten the association between the above mentioned factors and spontaneous recovery from aphasia. The following is a brief discussion of the evolution of stroke and possible recovery mechanisms in the brain.

Evolution of an Ischemic Stroke

Roughly three out of four strokes that result in irreversible loss of function are ischemic in nature. The remaining one-quarter are caused by cerebral hemorrhage, a condition which is more likely to lead to death than is ischemic stroke. Compared to cerebral hemorrhage, an ischemic stroke typically requires more straightforward medical treatment (Kalafut & Saver, 2000). It is more difficult to predict the progression of a cerebral hemorrhage than an ischemic stroke. Consequently, it is more difficult to predict the evolution of aphasia caused by a cerebral hemorrhage than an ischemic stroke.

Current knowledge of early physiological brain changes associated with stroke is in large measure derived from animal studies. In short, the onset of an ischemic stroke is accompanied by decreased protein synthesis in affected neurons, followed by anaerobic glycolysis, disruption of synaptic transmission,

and finally anoxic depolarization of cell membranes (Hossman, 1997). The ultimate extent of necrosis depends on the amount of blood flow in the affected area.

The Role of Thrombolytic Therapy in Stroke Evolution

Until recently the attempt to change the course of stroke and, ultimately, functional outcome was considered impossible (Kalafut & Saver, 2000). However, advances in thrombolytic therapy in hyper-acute stroke have largely changed this view (Hacke, et al., 1995; Hacke, et al., 1998; The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). It is now considered critical that patients receive medical treatment as soon as possible following the onset of an ischemic stroke. A report from the National Institute of Neurological Disorders and Stroke (NINDS; 1995) showed that administration of intra venous tissue plasminogen activator (IV-tPA) within three hours of stroke onset resulted in substantial benefit. This was preceded by research in animal models that demonstrated the effectiveness of IV-tPA in dissolving arterial blood clots with consequent improvement in function (Overgaard, Sereghy, & Boysen, 1992; Zivin, Fisher, DeGirolami, 1985; Zivin, Lyden, & DeGirolami, 1988). In addition, these studies revealed a strong relationship between the length of time from stroke onset and tPA administration and the incidence of intra-cerebral hemorrhage, a potential serious side effect of tPA. Arterial occlusion not only results in decreased perfusion to neural tissue but also increases the chance of

arterial-wall breakdown downstream from the occlusion. Following the promising results of the NINDS study, the United States Food and Drug Administration approved tPA as a therapeutic intervention in acute stroke when given within three hours of stroke-onset. Later studies have suggested that the tPA treatment window could in some cases be extended to six hours (Jansen, Schellinger, Fieback, Hacke, & Sartor, 1999; Kidwell, et al., 2000). These studies indicated that patients with a large hypoperfused area beyond a small lesion seen on diffusion weighted MRI could benefit from tPA when given as late as six hours post-onset of stroke.

The administration of tPA is not without controversy. In the 1995 NINDS study 6.4 percent of the experimental group who received tPA within 3 hours of symptoms developed an intracerebral hemorrhage following tPA administration compared to only 0.6 percent in the placebo group. Albers, Amarenco, Easton, Sacco, and Teal (2001) suggested that only about ten percent of stroke patients make it to the hospital within this three-hour window. After patients arrive at the hospital they must receive a specific work-up, including computerized tomography to screen out factors contraindicated for tPA administration such as cerebral hemorrhage. Even if patients may get to the hospital within the three hours it is not guaranteed that their work-up will be completed in time for them to receive tPA. Therefore, it is possible that some patients may actually get tPA after three hours from symptom onset, thereby increasing the chance of an intracerebral hemorrhage. Studies that have investigated the administration of

thrombolytics as late as six hours following symptom-onset suggest that the rate of cerebral hemorrhage is greatly elevated compared to control groups. For example, in the European Cooperative Stroke Study (ECASS; Hacke, et al., 1995) the percentage of tPA treated patients who developed an intra cranial hemorrhage was 19.8 compared to 6.5 in the placebo group.

Recovery Mechanisms in the Brain

It is not clear what factors drive recovery from aphasia, but several hypotheses have been set forth to explain this phenomenon. Prior to the 1960's, spontaneous recovery following brain damage was thought to be mediated by reorganization by which other cortical areas take over the function of the lesioned areas (reviewed by Finger, Le Vere, Almli, & Stein., 1988). This assumption was primarily based on Huglings Jackson's delineation of hemisphere equipotentiality. That is, even though left hemisphere lesions were more likely to result in aphasia than right hemisphere lesions, the right hemisphere played a role in automatic speech and could acquire the capability to process voluntary speech following brain injury. As will be discussed later, this view of recovery has been supported to some extent by recent neuroimaging studies of language processing in aphasia.

In the past three to four decades changes in perilesional areas have been recognized as factors in recovery following brain damage. Animal studies have revealed substantial collateral neural sprouting in tissue surrounding cortical lesions (Raisman, 1969; Loesche & Steward, 1977). Moreover, these

"regenerative (neuroplastic) phenomena were observed in adult mammals and seemed, in general, to obey principles of organization, growth, and guidance found in the nervous systems during development." (Stein & Glasier, 1992. p. 6).

Given that intra-hemispheric reorganization as well as significant collateral sprouting may take weeks, months, or even years (Stein & Glasier, 1992), it is probable that these mechanisms do not fully account for the significant spontaneous recovery often observed in the early phases of aphasia. In the 1980s, several studies suggested that an influx of the neurotransmitter glutamate around the lesion site resulted in increased necrosis and larger lesion size (Meldrum, 1985; Nieto-Sampedro, Manthrope, Barbin, Varon, & Cotman, 1983; Simon, Swan, Griffith, & Meldrum, 1984). Glutamate attaches to N-methyl-D-asparate (NMDA) receptors and is essential for normal brain functions such as learning and memory. Overabundance of glutamate kills neurons through overstimulation (Rothman, 1983; Scheinberg, 1991). Consequently, it is possible that changes in glutamate concentration around cortical lesions play an important role in determining the extent of recovery from aphasia (Shisler, Baylis, & Frank, 2000).

Neuroimaging Studies of Aphasia Recovery

Growing sophistication in neuroimaging has led to increased interest in macro analyses of recovery mechanisms in the brain. Using positron emission tomography (PET) Metter, et al. (1990) found that glucose metabolism in the angular gyrus and the temporal cortex correlated significantly with language

performance of aphasic persons. They suggested that the extent of hypometabolism was a better indication of language impairment than lesion size. In a similar study, Metter, Jackson, Kempler and Hanson (1992) found that increases in brain metabolism correlated with improvement in comprehension scores on the Western Aphasia Battery (WAB, Kertesz, 1982) within one-year post stroke. The initial scan for all of the patients studied by Metter, et al. was performed at least one-month post stroke.

Most studies of aphasia recovery, employing either PET or functional MRI (fMRI), have proposed that the bulk of cortical activation in the first weeks following stroke is localized to the right hemisphere. For example, Thulborn, Carpenter, and Just (1999) found that activation in the right hemisphere, homologous to Wernicke's and Broca's areas, greatly exceeded that of the left in a patient who received an fMRI scan within two days of a left frontal stroke. They concluded that the processing load had been shifted to the right hemisphere because of damage to language areas on the left. Others extended this interpretation to suggest that damage to language areas of the left hemisphere leads to a transfer of function from the left to the right hemisphere (Cao, Vikingstad, George, Johnson, & Welch, 1999). These studies further conclude that there is a gradual transfer of function back to the left hemisphere from the right in the weeks and months following stroke. That is, what is seen in spontaneous aphasia recovery appears to be that the left hemisphere gradually

reasserts its role in language processing, as edema around the cortical lesion decreases.

Nevertheless, it is unclear as to what role the right hemisphere plays in aphasia recovery following stroke. Gainotti (1993) suggested that right hemisphere contribution to aphasia recovery probably varies from one person to another, based on pre-morbid role of the right hemisphrere in language processing. If the right hemisphere assumes a larger role in language processing it seems logical that such a process would take a long time, rather then the few days suggested by Thulborn, Carpenter, and Just (1999). In addition fMRI studies using normal subjects have revealed that those areas of the right hemisphere that are homologous to language areas of the left, demonstrate increased blood flow during language processing compared to baseline. This raises the possibility that areas of the right hemisphere, which supposedly have assumed language function in the first few days following stroke, were possibly also involved in language processing before the stroke. Using fMRI, Carpenter, Just, and Reichle (2000) suggested that increased task difficulty results in increased activation in cortical areas involved in processing the task. Consequently, it is possible that the increased activation of the right hemisphere early post-stroke is the result of increased difficulty in language processing rather than a transfer of language function.

A significant limitation of fMRI and PET studies of aphasia recovery is inherent in the scanning methodology. Patients under study must complete at

least 10-15 minutes of on-line processing while in the scanner. Further, additional time is needed for T1- or T2-weighted structural MRI (T2-MRI) scans to be completed. From a medical standpoint, it may not be justifiable to leave patients who are immediately post stroke in an uncomfortable situation for such a long time.

Another limitation of MRI studies results from the inability of standard T1- and T2-MRI to reveal ischemic lesions sometimes as late as twenty hours after symptom onset (Fisher, Prichard, & Warach, 1995). Two relatively new MRI techniques – diffusion-weighted imaging (DWI) and perfusion imaging (PI) – overcome this limitation. DWI measures the rate of random diffusional movement of water (Brownian motion) in the brain and can detect hyperacute ischemia within minutes of stroke onset (Baird & Warach, 1998). Reduced blood flow in stroke results in a decrease in oxygen and glucose delivery to neurons and subsequently in reduction of adenosine triphosphate (ATP). ATP is the primary fuel for cellular energy and fuels the sodum-potassium pump. As ATP delivery ceases, the sodium-potassium pump stops working, leading to intracellular buildup of sodium. The end result is buildup of cytotoxic edema (cell swelling) because osmotically obliged water builds up within the cell, and ultimately ends in cell death (Moseley, et al., 1990). The buildup of intra-cellular water causes hypodiffusion. Using DWI makes it possible to visualize such hypodiffusion as a hyperintense region on the MR image. DWI is thought to show cortical matter that is no longer salvageable (Tong, et al., 1998). As dead tissue decreases in the

lesion scar, fluid restriction in the area decreases in the weeks and months following stroke. The lesion scar fills up with cerebral spinal fluid that is hyper-diffused in comparison to the surrounding tissue. The increase of water diffusion in the lesion scar poses a limitation on DWI, making it a poor technique for investigating stroke when diffusional movement of water in the lesion scar has reached the same or faster rate than in surrounding tissue. Equilibrium between lesion and surrounding tissue diffusion rate is thought to be reached, on average, at three days post-stroke (Helpern, et al., 1993; Knight, et al., 1991). Compared to DWI, T2-MRI appears to be a superior technique for lesion size investigation in sub-acute and chronic stages of stroke.

Perfusion Imaging (PI) provides information about microcirculation of blood in the brain. It is thought to make it possible to visualize neurons that are receiving just enough blood to survive, but not enough to function normally in addition to healthy, normal neurons (Barber, et al., 1998). Conventional PI tracks the passage of an injected paramagnetic bolus (gadolinium) through the brain, gathering repeated images over 90 to 120 seconds. By examining the passage of the contrast material through tissue it is possible to determine which areas are receiving adequate perfusion. This is because gadolinium takes longer to reach hypoperfused areas than healty tissue.

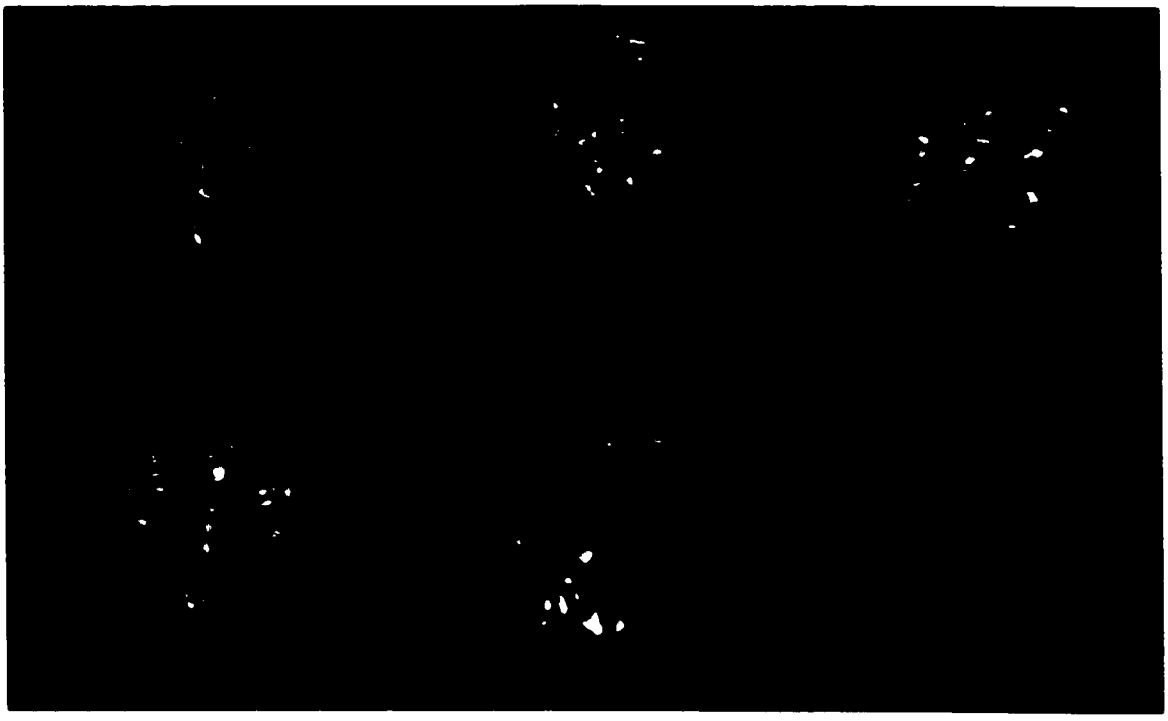
A recently developed perfusion imaging technique – arterial spin labeling (ASL-PI) – does not require a bolus injection (Detre & Alsop, 1999). ASL-PI makes it possible to differentiate areas of adequate perfusion from areas of

hypoperfusion by comparing images acquired following spatially different inversion of blood water molecules. Inversion refers to the collective transformation of molecules from a lower energy state (conventional state) to a higher energy state by emitting a radio frequency through tissue at an angle different from the direction of scanner magnetization. As the molecules return to the lower energy state they emit a signal that is detected by the MRI scanner. In short, two images are acquired in ASL-PI. Following inversion of water molecules in the large arteries that supply blood to the brain, the first image (labeled image) is collected. A second image (control image) is collected of the same slice but without a label. By subtracting the control image from the labeled-image, an image that is directly related to perfusion can be visualized. Several images are collected of the same slice and averaged together to increase power. Hypoperfusion is revealed as signal void on the ASL-PI image.

Several different ASL-PI techniques are available. The main difference between these techniques is based on labeled and control image timing and location. Flow-sensitive alternating inversion recovery (FAIR) is one version of ASL-PI. FAIR is based on collection of two labeled-images – one following global inversion and one following slice specific inversion. The difference between the images reflects differences in inflowing blood water. In short, hydrogen molecules are inverted (labeled) in a space covering the whole brain (global inversion) followed by acquisition of an image in the slice of interest. Another image is acquired following an inversion of hydrogen molecules in the

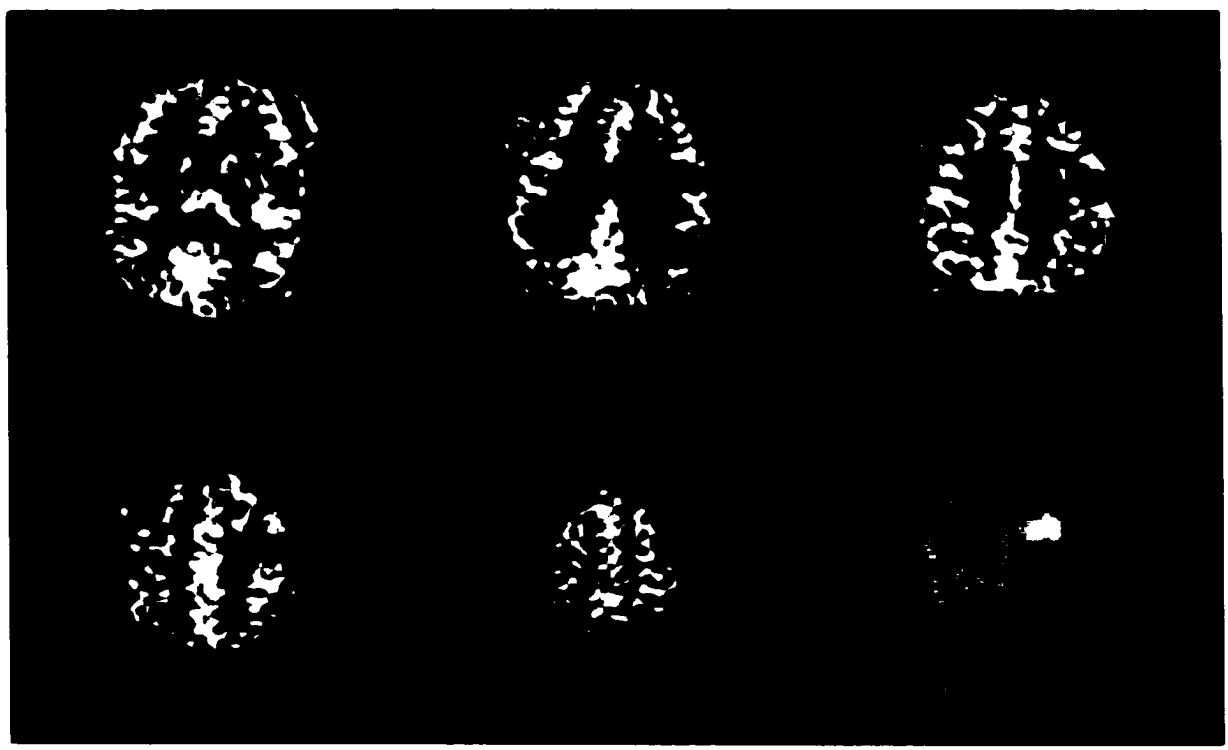
slice of interest (slice specific inversion). In slice specific inversion, water flowing into the slice is not inverted (the net molecule spin is not different from that in surrounding tissue), therefore affecting relaxation rate of inverted tissue water in the slice because of mixing of inverted and non-inverted water. However, inflow following global inversion is labeled, therefore influencing relaxation of tissue water less (inflow is labeled as well as blood water present in the slice). By subtracting images taken following slice-specific inversion from images taken following global inversion it is possible to produce a perfusion image (Figure 1).

Figure 1. ASL perfusion images (FAIR) of the brain of a 54-year old healthy woman



As mentioned earlier, blood takes longer to pass through hypoperfused tissue. Consequently, it will take longer for labeled blood to reach these areas than areas of adequate perfusion. Figure 2 shows FAIR and DWI images of the brain of a sixty-year old woman who suffered an embolic stroke to the left MCA. The images were taken twenty hours following the onset of symptoms. The lack of signal (signal void) on the perfusion image in the area of the lesion seen on the DWI image represents hypoperfusion.

Figure 2. ASL perfusion images (FAIR) and DWI image of the brain of a 60 year-old woman 20 hours post-stroke



When hypodiffused volume is subtracted from hypoperfused volume, an area called the "ischemic penumbra" can be seen (Schlaug et al., 1999). This area is considered to be potentially salvageable via treatment with tissue plasminogen activator such as t-PA (Marks, et al., 1999; Schellinger, et al., 2000). Further, this area may, in some cases, spontaneously resume blood flow that is sufficient for tissue to survive in the absence of intervention (Li, Silva, Sotak, & Fisher, 2000). Standard MRI techniques do not distinguish the ischemic penumbra from other parts of the brain that are adequately perfused (Neumann-Haefelin, Moseley, & Albers, 1999). Neither is it apparent on post-mortem analyses. Thus, PI reflects the remote effects of a stroke, giving a better picture of which areas are receiving inadequate perfusion at a given time.

One of the benefits of DWI and PI is that they make it possible to study the evolution of lesion size and its potential correlation with clinical outcome. DWI and PI take only a few minutes to complete and patients do not have to engage in a cognitive task in the scanner. Barber, et al., (1998) studied 18 patients within 24 hours, 5 days, and 84 days post stroke. They found that hypoperfused volumes were significantly correlated with acute neurologic state as measured by the Canadian Neurological Scale (Cote, Hachinski, Shurvell, Norris, & Wolfson, 1986), clinical outcome (as measured by the Barthel Index (Mahoney & Barthel, 1965)), and final infarct volume. Hypodiffused volumes did not correlate as highly with acute neurologic state as did hypoperfused volumes. Nevertheless, they correlated well with clinical outcome and final lesion volume.

In a similar study, Beaulieu, et al., (1999) studied 21 patients at five time points within 30 days post ischemic stroke. Their results largely concurred with those of Barber, et al., in that acute (< 7 hours) hypodiffused and hypoperfused volumes correlated well with initial neurological state, clinical outcome, and final lesion size.

In both studies, hypoperfused volumes had a higher correlation with clinical examination scores in acute care than did hypodiffusion volumes. Hypodiffusion and hypoperfusion volumes usually change substantially during the first few days following ischemic stroke. For example, a patient examined by Barber, et al. (1998) was shown to have 207 cm^3 of hypoperfusion and 13.8 cm^3 hypodiffusion when scanned within 24 hours of stroke onset. At seven days post-stroke these volumes had changed to 14.7 cm^3 and 44.2 cm^3, respectively. This patient showed significant recovery in function between the two MRI scans as revealed by scores on the Canadian Neurological Scale. In the Beaulieu, et al., study of 21 subjects, (1999) the average lesion size seen on DWI to be 44.67 cm^3 at day one. This average reached 134 cm^3 at one week post-stroke but decreased to 80.4 cm^3 at day 30. Mean hypoperfusion volumes remained relatively constant during the first two days after stroke but showed a gradual decrease in the following month. Of the 13 patients Beaulieu et al. scanned at 30 days post-stroke, four still had persistent hypoperfusion abnormality.

Finally, a study (N = 15) by Chalela, et al., (2000) revealed hypoperfusion abnormality in stroke patients to correlate significantly with NIHSS and Rankin

Scale scores. This study differed from the aformentioned studies in that it used ASL-PI instead of contrast bolus tracking for PI.

Questions and Hypotheses

Given the research to date, it appears to be fruitful to study the relationship between diffusion/perfusion and aphasia severity in the early phases of recovery. A close relationship may exist between changes in diffusion-perfusion post-ictus and recovery from aphasia. Spontaneous recovery in aphasia during the first weeks and months following stroke may reflect diffusion-perfusion dynamics. As areas of the brain involved in language processing receive enough blood to function they should begin to approximate pre-stroke status. As a precursor to prediction, it becomes important to establish whether there is a relationship between aphasia severity and hypoperfusion and hypodiffusion in early recovery.

The purpose of this study was to investigate this relationship in the early phases of recovery following a left middle cerebral artery (MCA) ischemic stroke. MCA strokes were studied because infarcts in areas irrigated by the left MCA are more likely to result in aphasia than infarcts of the anterior or posterior cerebral artery (Kertesz & McCabe, 1977).

The hypotheses that follow are based on the assumption that aphasia severity is related to the extent of cerebral hypoperfusion and lesion size. No causal assumptions about these relationships are made, because it is not presently possible to control the effect of lesion size on aphasia severity. Hypoperfusion is

expected to be a better predictor of aphasia severity than lesion size seen on DWI or T2-MRI. This is based on the observation that hypoperfusion usually extends beyond the actual lesion and may better reflect the extent of functional tissue than lesion size.

Further, previous studies of hemodynamics in stroke suggest that compared to the acute stage hypoperfusion volumes decrease over time but lesion size seen on DWI, and later on T2-MRI, increase over time. As pointed out by Holland (1989), most patients experience at least partial language recovery following stroke-induced aphasia. Consequently, the probability of a Type I error for the correlation analyses is increased simply because there is a linear trend in the study variables. A significant correlation may be observed even though, in the natural state, the variables may not be related. Traditionally, the alpha level in behavioral studies has been set at .05. Thus, to decrease the chance of Type I error in this study it is appropriate to use a more conservative alpha level than .05. The study questions and hypotheses were as follows:

Question 1. Does aphasia severity correlate with cerebral hypoperfusion and lesion size seen on DWI within 24 hours of symptom onset?

Hypotheses

H_0: Aphasia severity does not correlate with cerebral hypoperfusion and lesion size seen on DWI within 24 hours of symptom onset

H_1: Aphasia severity correlates with cerebral hypoperfusion and lesion size seen on DWI within 24 hours of symptom onset

Question 2. Does aphasia severity correlate with cerebral hypoperfusion and lesion size seen on T2-MRI at 30 days post-onset?

Hypotheses

H_0: Aphasia severity does not correlate with cerebral hypoperfusion and lesion size seen on T2-MRI at 30 days post-onset

H_1: Aphasia severity correlates with cerebral hypoperfusion and lesion size seen on T2-MRI at 30 days post onset

In some cases, decreased arousal may invalidate behavioral assessment of acute stroke patients. For example, a patient's decreased performance on an aphasia battery may reflect lack of attention during the test session rather than a language problem. In order to address this issue it seems important to assess a cognitive task that traditionally is thought to tax the non-dominant hemisphere. A differential diagnosis is made possible by a comparison between language and non-language performance. Test scores from this assessment would be expected to have lower correlation with the perfusion/diffusion data than aphasia severity scores. Therefore, the following secondary questions and hypotheses were addressed:

Secondary question 1. Does aphasia severity have higher correlation with hypoperfusion and lesion size seen on DWI than face discrimination ability within 24 hours of symptom onset?

Hypotheses

H_0: Aphasia severity does not have higher correlation with cerebral hypoperfusion and lesion size seen on DWI than face discrimination ability within 24 hours of symptom onset

H_1: Aphasia severity has a higher correlation with cerebral hypoperfusion and lesion size seen on DWI than face discrimination ability within 24 hours of symptom onset

Secondary question 2. Does aphasia severity have higher correlation with hypoperfusion and lesion size seen on T2-MRI than face discrimination ability at 30 days post-onset?

H_0: Aphasia severity does not have higher correlation with cerebral hypoperfusion and lesion size seen on T2-MRI than face discrimination ability at 30 days post onset

H_1: Aphasia severity has a higher correlation with cerebral hypoperfusion and lesion size seen on DWI than face discrimination ability at 30 days post onset

A final potential problem is presented by the timing of the initial assessment. Patients who have sustained an ischemic stroke often are very ill during the early phases of recovery. In addition, concerns about issues such as survival and subsequent chronic medical problems may further affect their mental status (Holland & Fridriksson, 2001). With that in mind, it is essential that

behavioral testing in the acute care take as little time as possible without giving up acceptable reliability and validity.

CHAPTER II - METHOD

Subjects

Nine patients served as subjects (Table 1). All subjects were scanned within 24 hours after estimated symptom-onset. The mean time between estimated start of symptoms and the MRI session was 15 hours with a standard deviation of 6 hr 18 min and range of 3 to 22 hours. All patients received behavioral testing within 25 hours after symptom onset. The mean time between estimated start of symptoms and testing was 16 hours with a standard deviation of 7 hr 22 min. The range was 4 hr 30 min to 25 hours.

All subjects had symptoms consistent with a left middle cerebral artery (MCA) ischemic stroke and were medically capable of MRI scanning at the time it was performed. One patient (RI, see below) received treatment with tPA within three hours of symptom onset.

Seven of the nine subjects were women. The mean age was 74.56 with a standard deviation of 3.68 and a range of 70 to 79 years. Seven subjects were Caucasian and spoke English as their first language. One subject was Native American. Her granddaughter reported that prior to the stroke, the subject spoke fluent English. One subject was Mexican-American.

Subjects with a history of moderate to severe dementia, seizure disorder, and whose primary language was not English were excluded from the study.

Table 1. Demographic data

Patients	Gender	Age	Ethnic background
RI	Man	79	Caucasian
EJ	Woman	74	Caucasian
CJ	Woman	77	Hispanic
EF	Man	77	Caucasian
MG	Woman	70	Native American
ES	Woman	70	Caucasian
LN	Woman	76	Caucasian
JT	Woman	70	Caucasian
PH	Woman	78	Caucasian

Sample Size

The sample size was based on results from Beaulieu, et al. (1999). The average effect size (Eta-squared) for their correlation analyses between hypodiffusion and hypoperfusion volumes and NIH Stroke Scale scores was .64 (Appendix A). Using that effect size as a reference, a power table was consulted (Table 2). According to Judd and McClelland (1989) a power of .60 or higher is considered ample for analyses in behavioral science, indicated by the shaded area on Table 2. Using a sample size of nine, the probabilities would be 0.70 and 0.86 of detecting effect sizes of .5 and .6, respectively. Given the effect size of Beaulieu, et al. (1999), a sample size of nine should have been adequate to detect an effect size as small as .5 if such a relationship existed between the study variables.

Table 2. Power table for correlation (Alpha = .05)

	True state of nature (or population correlation)					
	.1	.2	.3	.4	.5	.6
N – 1	Probability of significant correlation					
1	0.05	0.06	0.06	0.07	0.07	0.08
2	0.06	0.07	0.09	0.11	0.14	0.18
3	0.07	0.10	0.12	0.17	0.23	0.32
4	0.08	0.12	0.17	0.24	0.34	0.42
5	0.09	0.15	0.22	0.32	0.44	0.60
6	0.11	0.18	0.27	0.39	0.54	0.71
7	0.12	0.21	0.32	0.46	0.62	0.79
8	0.13	0.24	0.37	0.53	0.70	0.86
9	0.15	0.27	0.42	0.60	0.76	0.90
10	0.16	0.30	0.46	0.64	0.81	0.94
11	0.17	0.33	0.51	0.69	0.85	0.96
12	0.19	0.36	0.55	0.74	0.89	0.97

Procedure

Potential subjects for the study were identified through neurology-residents' morning reports that take place every weekday morning in the Department of Neurology at University Medical Center. Whenever patients were admitted to the hospital with the potential to be subjects in the study, they or their family members were asked by a neurology-resident whether they could be contacted by the investigator about participation in the study. All approached individuals agreed to be contacted by the investigator and signed a written informed consent[1]. After the consent was given, a brief language screen was conducted to determine if the potential subject had aphasia. Patients who qualified for the study underwent behavioral testing and perfusion imaging was added to their already scheduled MRI session that included DWI and T2-MRI.

[1] The study protocol was approved by the University of Arizona human subjects committee.

Depending on time constraints, behavioral testing was conducted within plus or minus three hours of the MRI session. At thirty days post-stroke, six subjects came back to UMC for another MRI session and behavioral testing.

Testing Immediately Post-Stroke – Language

The Bedside Evaluation Screening Test (2nd. ed.) (BEST-2; West, Sands. & Ross-Swain, 1998) served as the formal assessment tool. The BEST-2 takes about 15-20 minutes to administer and was "designed for use when assessing patients in the early stages of recovery from aphasia when they may not be physically able to respond to a full aphasia assessment battery." (West, Sands, & Ross-Swain, 1998, p. v). There are seven subtests on the BEST-2 focusing on: 1) Conversational Expression; 2) Naming Objects; 3) Describing Objects; 4) Repeating Sentences; 5) Pointing to Objects; 6) Pointing to Parts of a Picture; and 7) Reading. Each of the subtests has five items and a maximum score of thirty. Raw scores can be converted to percentile ranks and standard scores and the sum of standard scores is used to rate subjects' aphasia severity (> 91 = No Impairment; 77-91 = Mild; 63-76 = Moderate; < 63 = Severe). Standard error of measurement (SEM) based on a sample of 164 patients with primary diagnosis of cerebrovascular accident is within .85 on each of the subtests (maximum score for each subtest is 30).

Testing Immediately Post-Stroke -- Florida Affect Battery

The Florida Affect Battery (FAB; Bowers, Blonder, & Heilman, 1991) was used for assessment of a non-language behavior that is thought to tax the non-dominant hemisphere. The FAB was designed to assess the perception of facial affect using a variety of tasks on ten different subtests.

Only one FAB task was administered in this study – Subtest 1: Facial Identity Discrimination. On this task, subjects were shown pairs of black-and-white photographs of unfamiliar faces and had to determine whether the faces were the same or different. The faces were presented two per page in a vertical array. There are two practice items and twenty test items on this subtest. Subjects were provided cards with the words "same" or "different" written on them in order to respond non-verbally. For subjects who needed to use this non-verbal response option, three practice items with pictures of "same" or "different" geometric shapes were used to train a consistent response.

Testing Immediately Post-Stroke – National Institutes of Health Stroke Scale

Most studies that have investigated the relationship between hypoperfusion, lesion size, and neurological status have used the National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989) (Beaulieu, et al., 1999; Chalela, et al., 2000, Lovblad, et al., 1997; Tong, et al., 1998). The NIHSS is used as a guideline for the neurological exam of stroke patients and is usually administered upon patient admission. There are several versions of the NIHSS

available. The version used in this study was employed in the NINDS tPA stroke trial (1995). It includes eleven areas that focus on level of consciousness, gaze, visual fields, facial palsy, motor function of arms and legs, limb ataxia, sensory function, language, dysarthria, and neglect. Items are scored on rating scales ranging from 0-2 points to 0-9 points. The higher the score on the NIHSS, the greater the neurological impairment. In order to compare the present data to results from other studies all subjects were assessed an NIHSS score within 24 hours and again at 30 days post-stroke.

Testing at One-Month Post-Stroke

Each subject was evaluated again at one-month post-stroke using the BEST-2, FAB, and NIHSS. In addition, in order to describe residual language problems more explicitly, all subjects who were re-evaluated for aphasia at one month post-stroke were administered the short from of the recently re-standardized Boston Diagnostic Aphasia Examination (3rd. Ed) (BDAE; Goodglass, Kaplan, & Barresi, 2001). The short form of the BDAE takes about thirty minutes to administer and tests subjects' auditory comprehension, verbal expression, reading, and writing abilities. Subjects were also administered the 15-item short form of the Boston Naming Test (2nd. Ed.) (BNT; Kaplan, Goodglass, & Weintraub, 2001) which is included as a part of the revised BDAE.

Magnetic Resonance Imaging

MRI was carried out on a General Electric 1.5 Tesla scanner. Perfusion imaging, using arterial spin labeling (ASL-PI), was added to the scanning sessions of the subjects selected for this study. This increased the total scanning time by about five minutes. The ASL-PI technique used for this study was Flow-sensitive Alternating Inversion Recovery (FAIR; Kwong, et al., 1995). The field of view (FOV) was set at 30 cm X 30 cm with a grid of 128 X 128 pixels. TR was set at 10.000 ms and TE effective at 96 ms. Time between inversion and image acquisition was set at 1,400 ms. Perfusion images were transferred from the MRI console to a Sun Microsystems computer for analyses. Fifty images were collected for each of five slices following slice-specific inversion and fifty following global inversion on pair-by-pair bases. Subtractions were performed within each image pair (slice-tagged image minus globally-tagged image). Images resulting from these subtractions were averaged together to generate a composite perfusion image.

Perfusion Weighted Images

As mentioned earlier, Arterial Spin Labeling PI is a new imaging technique that holds much promise for neuroimaging. However, it is not without limitations. After blood water in distal blood vessels is labeled (inverted) the label persists for a maximum of 3-4 seconds. Thus, blood water that is imaged after this time-period following inversion is not labeled. Moreover, if blood takes

more than two seconds to go from major blood supplying arteries to brain areas of interest ASL-PI cannot reveal perfusion in these areas. To work within this constraint, only five slices were used for perfusion imaging. Slice thickness was set at 7 mm with 2 mm gap between slices covering a 4.3 cm thick area for perfusion imaging. In cases when hypoperfusion is apparent in the lowest PI slice it is impossible to estimate the total volume of hypoperfusion because it is not known how far hypoperfusion extends below the lowest slice.

Perfusion images were analyzed using Khoros software on a Sun Microsystems computer. Khoros is a multi-purpose visual programming software that makes it possible to process images in gray scale. Using Khoros, raw images were scaled with values from 0-200. The perfusion image of a corresponding slice was noise filtered and the remaining signal (theoretically corresponding to perfusion) was turned into a binary image in which perfused areas were given a value of 400. After both images were color scaled to give low values as brighter colors and higher values as darker colors, the binary image was overlaid on top of the raw image. Because the perfusion image had higher values than the raw image it was possible to visually distinguish between the two images. The raw image was then used as a reference for manual outlining the hemispheres. After the outline had been drawn, the raw image was subtracted from the composite perfusion image. This permitted counting of voxels with a positive signal. This procedure was followed for both hemispheres. Inter-rater reliability for image outlining was estimated by calculating the correlation between the number of

voxels reported for each image by the primary investigator and a second investigator who was blinded to the purpose of the study. The correlation (Spearman) between voxel numbers reported for each image by the two investigators was .98 ($p = .0001$).

To date, analyses of perfusion MRI data have mainly been qualitative in nature. That is, hypoperfusion can be imaged using MRI but reliable quantitative measures have not been developed to assess the extent of perfusion abnormality. To quantify perfusion in this study, a ratio of left hemisphere PI pixels over the whole brain PI pixels was calculated (left/whole hemisphere perfusion ratio). Thus, the right hemisphere was used as a referent for subjects' cerebral perfusion. In case of a large perfusion deficit in the hemisphere that incurred the ischemic event, a lower ratio would be expected than in cases in which there is only very limited or no hypoperfusion. A similar method was used by Chalela et al. (2000) to quantify perfusion. However, instead of comparing the difference in signal between the two hemispheres, they compared the mean signal intensity between the two hemispheres. In cases of luxury (hyper) perfusion in the stroked hemisphere this may not be an optimal method to quantify perfusion in stroke. Significant luxury perfusion could increase the average signal intensity of the stroked hemisphere and confound the inter-hemispheric comparison. Also, when perfusion is reduced bilaterally this method will underestimate hypoperfusion in the stroked hemisphere.

In order to compare the perfusion ratios found in this study to what is found in normal brains, three normal subjects were scanned with the perfusion MRI. The perfusion ratios for these three subjects were .5013, .5091, and .5003. These ratios indicate minimal difference in cerebral perfusion between the two hemispheres as measured in this study.

Diffusion Weighted Images

For DWI, 22 slices were collected using single-shot Echo Planar Imaging (EPI). Slice thickness was set at 5 mm without inter-slice gaps. As with the PI images the field of view was set at 30 cm X 30 cm with a grid of 128 X 128 pixels. TR was set at 10,000 ms and TE effective at 96 ms. Lesion volume analyses were performed, again using Khoros software on a Sun Microsystems computer. DWI slices were visually inspected for evidence of hypodiffused lesion. Using grey-scale, it was possible to visually distinguish between a voxels with very high values compared to surrounding tissue having considerably lower values. By drawing a rough outline of the lesion it was possible to calculate the mean voxel value as well as its standard deviation. The image was high-pass filtered at two standard deviations below the mean voxel value for the lesion. A reference image was used to ensure that over- or under-filtering did not take place. The number of lesion-voxels was multiplied by the voxel dimensions to obtain lesion volume.

Finally, all subjects underwent T2-MRI imaging. Slice thickness was set at 5 mm (1.5 mm gap between slices) with a TR of 90 ms and a TE of 24 ms. Field of view was 22 cm X 16 cm and the grid was 256 X 192. Volume analyses were performed in the same way as on DWI except that low pass filtering was used to remove signal from cerebral spinal fluid.

Data Analyses

Spearman rank correlation coefficients were calculated for correlations between standard scores from the BEST-2, BNT scores, NIHSS scores, perfusion ratios, and lesion volumes seen on DWI and T2-MRI. This non-parametric test was used because of the small sample size. Alpha level was set at .01. Because most subjects scored within normal limits on the FAB point-biserial correlations were calculated between raw scores on the FAB and other variables used in the study. That is, subjects performance was scored as being below or within normal limits.

Results from the BDAE and informal language probes were used to describe subjects more explicitly and to discuss subjects with different extents of recovery from aphasia.

CHAPTER III – RESULTS

The preceding chapters discussed the importance of investigating the relationship between perfusion, diffusion, and aphasia severity in the early phases of stroke as well as the method for the present study. This chapter describes the study results and, briefly, how they relate to the study hypotheses. First, results that pertain to findings in the acute stage of stroke will be discussed followed by findings at one-month post-stroke.

Results Immediately Post Stroke – Language Testing

Standard scores from the BEST-2 ranged from 36 (severe) to 76 (mild) (Appendix B). A score of 93 and above indicates no impairment. The mean score was 63 with a standard deviation of 14.21. A range of aphasia types was noted. For example, CJ had global aphasia and could only produce a few stereotypical utterances. In contrast, LN had anomic aphasia and merely experienced intermittent word finding difficulty in conversation. Appendix C contains brief case reports of subjects examined in the study. Starting in acute care, all subjects were followed during the month following stroke – some were followed beyond the one-month period post-stroke. The case reports summarize subjects' backgrounds, pertinent medical information, and the results of behavioral testing.

Results Immediately Post Stroke – FAB and NIHSS

All subjects performed above chance level on the FAB. In fact, most subjects made only one or two errors. The mean score was 19 and the range was 13 to 20. Three

subjects responded correctly to all 20 items and three made only one mistake. Two subjects (EF & CJ) completed the FAB nonverbally. EF missed only one item. CJ was correct on 13 of 20 items.

An NIHSS score was determined for each subject upon arrival to the emergency room by a neurology resident. The mean score was 5.2 with a standard deviation of 2.33 and a range of 3-11. Based on neurology residents' judgement, no subject's NIHSS scores changed between the initial assessment in the emergency room and the assessment repeated at the time of the MRI.

Results Immediately Post Stroke – Imaging data

Perfusion deficits were visually obvious in the left hemisphere of all subjects (Appendix D). Hypoperfusion ranged from involving only the immediate lesion (subject PH) to affecting most of the left hemisphere (subject CJ). Visual inspection of the PI scans suggested right hemisphere hypoperfusion deficit in the brain of four subjects (EF, CJ, EJ, and JT).

Quantitative data analyses were also performed on the PI data. The mean for the left/whole hemisphere perfusion ration was .4309 (SD = .0642) with a range of .33 to .50.

Lesion size seen on DWI was not a significant predictor of left/whole hemisphere perfusion ratio (left/whole perfusion ratio = .45 - (lesion size on DWI).0004, $F = 1.62$, $p = .244$). This was not surprising since visual inspection suggested that a small lesion seen on DWI was not always associated with small area of hypoperfusion. For example, CJ had two lacunar infarcts but a large portion of the left hemisphere was hypoperfused.

In contrast, the DWI scan for PH showed a wedge shaped lesion in the left frontal lobe but the PI scan showed only minor abnormality in the area of the actual lesion. That is, based on the DWI and PI scans, no ischemic penumbra was seen in the brain of this subject.

Results Immediately Post Stroke – Correlations

A series of Spearman correlations addressed the relationship between BEST-2 scores, NIHSS scores, left/whole brain perfusion ratios, and lesion volumes seen on DWI (Table 3). Point-biserial correlations were calculated between FAB scores and other study variables. The correlation was found to be statistically significant between BEST-2 scores and left/whole brain perfusion, r (9) = .80, p = .005. Consequently, aphasia severity, as measured in the present study appears to correlate with cerebral hypoperfusion ratio within 24 hours of symptom onset. The relationship between aphasia severity and hypoperfusion ratio is further highlighted in Figure 3. As can be seen on this graph a low left/whole brain perfusion ratio indicates more severe aphasia. Conversely, subjects whose perfusion ratio was closer to .50 tended to have less severe aphasia than those with more significant left hemisphere hypoperfusion. These results suggest that decreased perfusion in the left hemisphere of aphasic subjects is a predictor of increased aphasia severity.

The Spearman correlation coefficient for the relationship between BEST-2 scores and lesion size measured on DWI did not reach statistical significance (r (9) = -.22, p = .287) (Figure 4). There did not appear to be a clear relationship between lesion size and

aphasia severity. That is, subjects with larger lesions did not appear to have more severe aphasia than those who had smaller lesions. CJ and EJ, who had small (lacunar) infarcts, did not have mild aphasia. CJ had global aphasia but lesion volume of 4 cm^3. In contrast, LN had mild anomia but a lesion size that was considerably larger (22 cm^3) than CJ's.

The point-biserial correlation was r (9) = .32, p = .20, between FAB scores and left/whole brain perfusion and r = -.32, p = .20, for FAB scores and lesion volume seen on DWI. Neither of these correlation coefficients exceeded those for the relationship between BEST-2 scores and lesion data suggesting that, for these subjects, language function was more affected by stroke than face discrimination ability. This was an important finding because if this had not been the case, decreased performance on the BEST-2 could have reflected decreased attention and/or arousal rather than aphasia severity. It is also important to note that most subjects had a perfect or near perfect score on the FAB. This was clearly not the case for subjects' performance on the BEST-2, providing justification for differential diagnosis of aphasia rather than some more general cognitive impairment.

Table 3. Correlation matrix for data collected immediately post-stroke

BEST-2	1.000 . 9				
FAB	.14† .35 9	1.000† . 9			
NIHSS	.372 .162 9	.42† .11 9	1.000 . 9		
Lesion size seen on DWI	-.218 .287 9	-.32† .20 9	.587* .048 9	1.000 . 9	
Left/whole ratio	.803** .005 9	.32† .20 9	.345 .182 9	-.317 .203 9	1.000 . 9
	BEST-2	**FAB**	**NIHSS**	**Lesion size**	**Left/whole ratio**

* Correlation is significant at the .05 level (1-tailed)

** Correlation is significant at the .01 level (1-tailed)

† Point-biserial correlation

Figure 3. Association between BEST-2 scores and left/whole brain perfusion immediately post-stroke

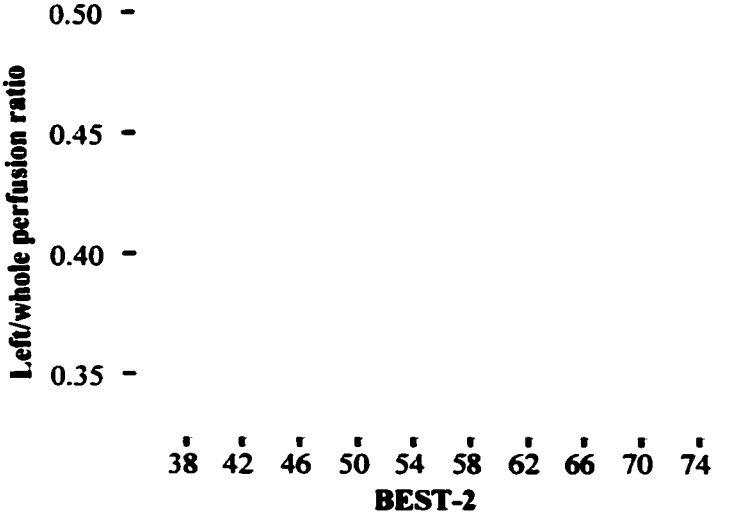
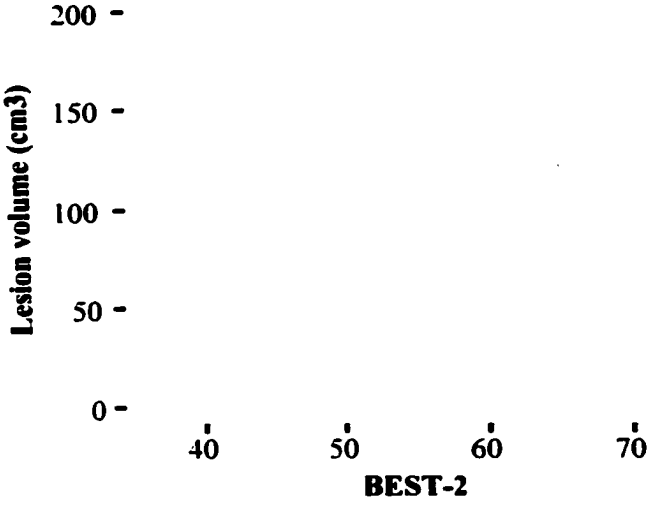


Figure 4. Association between BEST-2 scores and lesion volume seen on DWI immediately post-stroke



The Spearman correlation coefficient did not reach statistical significance for the relationship between NIHSS scores and left/whole brain perfusion, r (9) = -.35, p = .18. There was a significant correlation between NIHSS scores and lesion size seen on DWI, r (9) = .59, p = .048, at an alpha level of .05. This implies that, for these nine subjects, lesion size was a better predictor of overall neurological impairment than was the left/whole brain perfusion ratio. Large lesions seen on DWI appear more likely to be associated with higher scores on the NIHSS (higher score indicates increased neurological impairment) than lower perfusion ratios.

Results at One-Month Post-Stroke – Language Testing

Seven of nine subjects were tested with the BEST-2, FAB, BDAE, and BNT at one-month post-stroke. One subject declined reassessment and one died following a second massive stroke involving the cerebellum and brainstem. The mean score on the BEST-2 on reexamination was 82 with a standard deviation of 13 and a range of 63 to 93 (Table 4). Six of these seven subjects obtained higher scores compared to the initial assessment. Three scored within normal limits, one had only mild anomia, one had Broca's aphasia, and one had conduction aphasia. One subject (ES) did not improve nor did her aphasia evolve to another type. She also demonstrated increased phonemic paraphasias in naming and running speech. The mean improvement on the BEST-2 was 14.42 (SD = 11.23). A within-group t-test revealed a statistically significant difference between BEST-2 scores immediately post-stroke and at one-month post-stroke, t (6) = 3.33, $p < .016$ BEST-2 scores in acute care and at one-month post-stroke were also compared nonparametrically. The Wilcoxon signed-rank test also revealed a statistically significant difference between the groups using an alpha level of .05 (n = 7, $T = 2.213$, $p < .027$), once again indicating substantial recovery from aphasia. For example, PH demonstrated transcortical motor aphasia in acute care, but tested within normal limits at one-month post-stroke. JT was similar, in acute care she made phonemic paraphasias in almost every sentence but reported no difficulty with language upon re-examination.

[2] All following t-test comparisons were also performed using Wilcoxon signed-rank test. Unless specified in the text, these comparisons were not different from t-test results.

Table 4. Performance on language tests and aphasia types

Subj-ects	Day 1 Aphasia type	Day 30 Aphasia type	Day 30 BNT	Day 1 BEST-2	Day 30 BEST-2	BEST-2 change
EF	Wernicke's	Died		36*	Died	
CJ	Global	Broca's	4†	45	63	18
MG	Broca's	Declined reassessment		56	Declined reassessment	
RI	Anomic	Anomic	11	65	82	17
EJ	Conduction	Conduction	12	67	84	17
JT	Conduction	WNL	13	69	91	22
PH	Trans. Mot.	WNL	14	74	93	19
LN	Anomic	WNL	10	76	93	17
ES	Conduction	Conduction	6	76	65	-11

* Maximum score possible is 100
† Maximum score possible is 15

In contrast to performance on the BEST-2, at one-month post-onset no subject correctly named all items on the Boston Naming Test (BNT). The mean score on the BNT was 10 with a standard deviation of 3.7 and a range of 4 to 14 (out of 15 possible). Finally, administration of the BDAE provided a more detailed language profile of each subject (Appendix E). However, results from the BDAE were not used for statistical comparisons. Rather, these results were used to more clearly describe subjects when aphasia had become a more chronic condition. Patients' performance on the BDAE is further described in Appendix C – Case Reports.

Results at one-month post-stroke – FAB and NIHSS

The mean score on the FAB on reexamination was 18.14 with a standard deviation of 2.03 and a range of 14 to 20 (Table 5). Two subjects responded correctly to

all 20 items and four made only one or two mistakes. The mean improvement for the group was .57 (SD = 1.6). The difference between FAB scores immediately after stroke and at one-month post-stroke was not statistically significant (t (6) = .93, $p < .39$), largely because of the ceiling effect obtained in acute care. Again, ES was the only subject who received a lower score at one-month post-stroke compared to acute care.

Six of seven subjects improved on the NIHSS at one-month post-stroke (low score = less neurological impairment). The only unchanged subject was ES whose aphasia also did not improve. Because most subjects had relatively low scores immediately post-stroke, there was little room for improvement. In fact, two subjects' NIHSS scores were normal and one subject was within one point of normal. The difference between NIHSS scores in acute care and on reassessment was statistically significant, t (6) = 4.0, $p < .007$. At one-month post-stroke most subjects appeared to have re-established their pre-stroke routines. PH, for example, drove herself to UMC for the follow-up exam and was planning to see a movie after the examination.

Table 5. FAB and NIHSS scores immediately and at one-month post-stroke

	Day 1	Day 30		Day 1	Day 30	
Subjects	FAB	FAB	FAB Change	NIHSS	NIHSS	NIHSS change
EF	19	Died		4	Died	
CJ	13	14	1	11	6	-5
MG	19	Declined reassessment		5	Declined reassessment	
RI	15	18	3	5	3	-2
EJ	16	18	2	4	3	-1
JT	20	20	0	3	0	-3
PH	19	19	0	5	1	-5
LN	20	20	0	4	0	-4
ES	20	18	-2	6	6	0

Results at One-Month Post-Stroke – Imaging Data

Six of the seven subjects who were evaluated at one-month post-stroke received an MRI. EJ refused the MRI scanning session because of claustrophobia. Compared to day one, visual inspection suggests that cerebral perfusion had increased for all of the subjects except ES who had marked decrease in global perfusion at one-month post-stroke that was accompanied by the previously mentioned marked increase in aphasia severity, and no change on the NIHSS. The mean left/whole perfusion ratio at one-month post-stroke was .46 with a SD of .038 (Table 6). The range was .40 to .51. The difference between left/whole brain perfusion ratios immediately post-stroke and at one-month post stroke was not statistically significant, t (5) = .92, $p < .40$. Four of six subjects' perfusion ratio did improve at one-month post-stroke. That is, compared to right hemisphere perfusion, left hemisphere perfusion had increased. Based on results from these subjects, left hemisphere perfusion would be expected to improve in the month following stroke, even in the absence of tPA administration. Greatest increase in perfusion was observed in the brain of CJ, who did not receive tPA. RI, who was the only subject who was treated with tPA, also had increased perfusion at one-month post-stroke. Both of these subjects experienced marked recovery from aphasia. In contrast, ES' scan showed a decline in global perfusion as well as a less favourable perfusion ratio. This change was, again, accompanied by an increase in aphasia severity.

Hyperintensity was visually apparent on T2-MRI scans of five subjects at reexamination. An increase in lesion size was observed for CJ, PH, LN, and ES

compared to immediately post-stroke. This change was very substantial for ES, who along with CJ, still had a marked hypoperfusion deficit at one-month post-stroke. In comparison, RI had a significant decrease in actual lesion size (DWI minus T2-MRI) at one-month post-stroke compared to what was seen on MRI in acute care. The difference in lesion size immediately post-stroke and at one-month post-stroke was not statistically significant (t (5) = 1.35, p < .23). It is important to reiterate that RI was the only subject who was treated with tPA and that he was the only subject whose measured lesion size decreased at one-month post-stroke.

Table 6. Perfusion and lesion size immediately post-stroke (DWI) and at one-month post-stroke (T2-MRI)

	Day 1	Day 30		Day 1	Day 30	
Subjects	Perfusion ratio	Perfusion ratio	Change in ratio	Lesion size	Lesion size	Change in lesion size
EF	.34	Died		201 cm^3	Died	
CJ	.33	.40	.15	4 cm^3	124 cm^3	+120 cm^3
MG	.39	Declined reassessment		25 cm^3	Declined reassessment	
RI	.42	.48	.06	123 cm^3	92 cm^3	-31 cm^3
EJ	.49	Declined reassessment		3 cm^3	Declined reassessment	
JT	.47	.49	.02	0 cm^3	0 cm^3	0 cm^3
PH	.46	.51	.05	52 cm^3	55 cm^3	+3 cm^3
LN	.45	.44	-.01	22 cm^3	53 cm^3	+31 cm^3
ES	.50	.46	-.04	43 cm^3	395 cm^3	+352 cm^3

Results at One-Month Post-Stroke - Correlations

A series of Spearman correlation coefficients were calculated between standard scores from the BEST-2, BNT scores, NIHSS scores, left/whole brain perfusion ratios, and lesion volumes seen on T2-MRI (Table 7). Again, point-biserial correlation coefficients were calculated between FAB scores and other study variables. The correlation between BEST-2 scores and left/whole brain perfusion (Figure 5) was not

statistically significant (r (6) = .49, p = .16). However, inspection of perfusion images suggests that brains of subjects with the lowest BEST-2 scores (ES and CJ) were significantly hypoperfused at one-month post-stroke. On the other hand, PH, JT, and LN scored within normal limits on the BEST-2 and also had perfusion ratios compatible to what is seen in normal subjects. These results are similar to what was found in the acute stage. That is, lower left hemisphere perfusion is more likely to be associated with more severe cases of aphasia.

The correlation between BEST-2 scores and measured lesion size seen on T2-MRI (Figure 6) did not reach statistical significance (r (6) = -.75, p = .042) for an alpha level of .01. Subjects with larger lesions were, however, more likely to have more severe aphasia than subjects who scored within normal limits on the BEST-2 at one-month post-stroke. ES who had the second lowest score on the BEST-2 had, by far, the largest lesion seen on T2-MRI and CJ who scored lowest on the BEST-2 had the second largest lesion.

There was a strong correlation (r (6) = .89, p = .009) between BNT scores and left/whole brain perfusion (Figure 7). Because no subject achieved a perfect score on the BNT, this measure probably reflects aphasia severity more accurately at one-month post-stroke than BEST-2 scores. These results further support previous findings that low perfusion ratios are associated with more severe aphasia than when perfusion in the left hemisphere is similar to right hemisphere perfusion.

The correlation between lesion size and BNT scores was not statistically significant, r (6) = -.66, p = .078. However, this relationship approached statistical significance and is similar to that found for the relationship between lesion size and

BEST-2 scores at one-month post-onset. That is, for the subjects examined in this study, large lesions were more likely to be associated with more severe aphasia than smaller lesions at one-month post-stroke.

Table 7. Correlation matrix for assessment at one-month post-stroke

BEST-2	1.000 . 7					
FAB	.878**† .005 7	1.000† . 7				
NIHSS	-.898** .003 7	-.92**† .002 7	1.000 . 7			
BNT	.721* .034 7	.23† .31 7	-.642 .060 7	1.000 . 7		
Left/whole ratio	.493 .160 6	.42† .18 6	-.265 .306 6	.886** .009 6	1.000 . 6	
Lesion size seen on T2-MRI	-.754* .042 6	-.46† .15 6	.971** .001 6	-.657 .078 6	-.257 .311 6	1.000 . 6
	BEST-2	**FAB**	**NIHSS**	**BNT**	**Left/whole Ratio**	**Lesion size**

** Correlation is significant at the .01 level (1-tailed)

* Correlation is significant at the .05 level (1-tailed)

† Point-biserial correlation

Figure 5. Relationship between BEST-2 scores and left/whole brain perfusion at one-month post-stroke

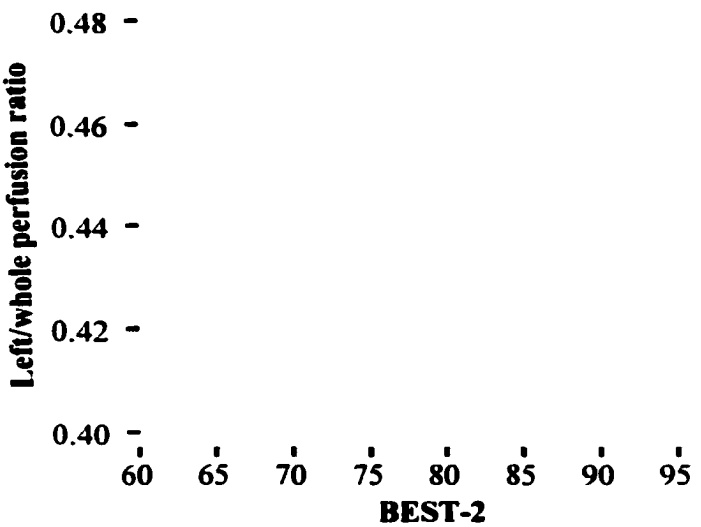


Figure 6. Relationship between BEST-2 scores and lesion size seen on T2-MRI at one-month post-stroke

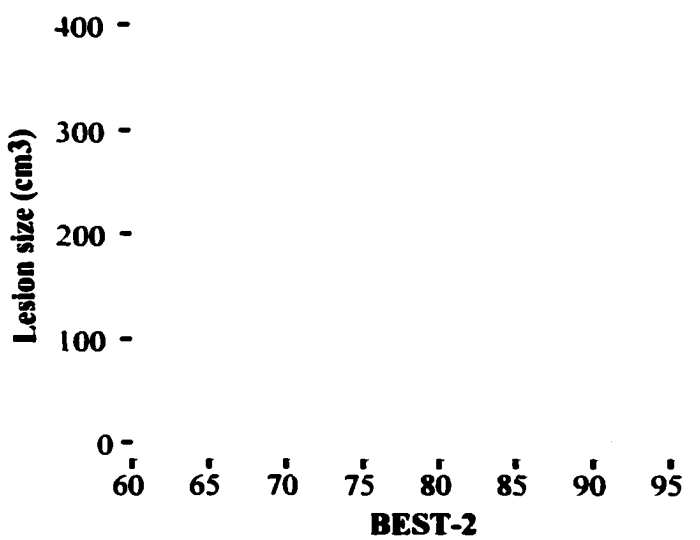
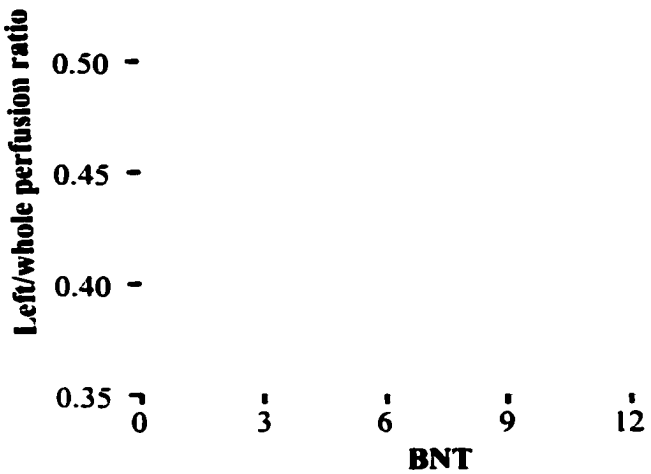


Figure 7. Relationship between BNT scores and left/whole brain perfusion at one-month post-stroke



The point-biserial correlation between FAB scores and left/whole perfusion was not statistical significant (r (5) = .42, p = .18). As was the case at day 1, the correlation between FAB scores and hypoperfusion (.27) was lower than the correlation between BEST-2 scores and hypoperfusion (.49). This was also the case for the relationship between FAB scores and lesion size seen on T2-MRI (r (6) = -.46, p = .15). The correlation between BEST-2 scores and lesion size was -.74. Because most subjects scored high on both the BEST-2 and FAB, it is difficult to decipher the importance of these results. At least, it is clear that subjects improved on both the BEST-2 and the FAB but that the improvement was much greater on the BEST-2.

NIHSS scores did not correlate significantly with left/right brain perfusion (r (6) = -.27, p = .306). There was a strong correlation, however, between lesion size seen on T2-MRI and NIHSS scores (r (6) = .97, p = .001). The only subjects who still had significant neurological findings beyond aphasia at one-month post-stroke were ES and CJ. Both had right visual field neglect and ES had mild right facial palsy. These subjects also had the largest lesions seen on T2-MRI at one-month post-onset.

In summary, these results suggest that for subjects included in this study, increased hypoperfusion as evaluated by visual inspection was associated with more severe aphasia in the acute stage and at one-month post-stroke. Lesion size was significantly correlated with aphasia severity at one-month post-stroke but not in the acute stage. FAB scores provided important information for differential diagnoses because most subjects showed minimal improvement in facial discrimination ability compared to recovery from aphasia.

CHAPTER IV - DISCUSSION

Above, study results were presented along with brief interpretations of what these findings mean. Below are further delineations of how these results relate to the study questions and to findings of other investigations of aphasia severity.

Question 1

> Does aphasia severity correlate with cerebral hypoperfusion and lesion size seen on DWI within twenty-four hours of symptom onset?

A statistically significant correlation between aphasia severity and hypoperfusion in acute stroke suggests that left hemisphere perfusion is related to aphasia severity. PI scans in Appendix D are ordered according to subjects' aphasia severity level in the acute stage. The relationship between hypoperfusion and aphasia severity is apparent even through visual inspection of these PI scans. Subjects with the lowest BEST-2 scores in the acute stage – EF, CJ, and MG – clearly have less left hemisphere perfusion than subjects with milder aphasia (e.g. PH & ES). CJ and EF both had severe aphasia as well as the lowest left/whole brain perfusion ratios of the study group. Conversely, higher ratios were associated with higher scores on the BEST-2. Based on these results it is reasonable to suggest that subjects whose acute stroke results in significant dominant hemisphere hypoperfusion are more likely to have severe aphasia in the acute stage than those whose hypoperfusion involves less cortex. This is similar to findings of Cappa et al. (1997) who used positron emission tomography (PET) to investigate eight stroke subjects with mild aphasia. Lower metabolism in the left hemisphere at two weeks and

six months following stroke was found to correlate with aphasia severity. In addition, employing six aphasic subjects, Heiss et al. (1997) found decreased metabolic rate in the left hemisphere to be related to both aphasia severity and recovery. This study also utilized PET. These two studies and the present investigation differ in that neither of the previous studies concerned subjects with acute stroke.

The present findings also concur with studies of hypoperfusion and global neurological impairment (Barber, et al., 1998; Beaulieu, et al., 1999; Chalela, et al., 2000; Lev, et al., 2001; Neumann-Haefelin, et al., 1999; Tong, et al., 1998). These studies used repeated scans and behavioral assessment of stroke patients within the first month of onset – usually starting in acute care. Even though none specifically studied aphasia, they all suggest that decreased cerebral perfusion in the stroked hemisphere is associated with increased neurological impairment. For example, using ASL-PI, Chalela et al. (2000) found a strong correlation (Spearman; $p = .007$) between left/right MCA perfusion difference and neurological impairment measured on the NIHSS in 15 acute stroke patients. Similar to the present study, subjects who had the greatest difference in left and right hemisphere perfusion had poorer neurological status overall than subjects with smaller hemisphere differences.

In contrast to the relationship between hypoperfusion and aphasia severity, there did not appear to be a clear link between lesion size and aphasia severity in the subjects studied here. Lesion size seen on DWI varied greatly between the subjects. Small lesions were not necessarily associated higher scores on the BEST-2. PH, for example, had a considerably larger lesion (52 cm^3) than CJ (4 cm^3) but her stroke resulted in

aphasia that was not nearly as severe as CJ's. The correlation between lesion size and hypoperfusion was not statistically significant which suggests that larger lesions were not always associated with low left/right perfusion ratios and increased aphasia severity – "what you see (on DWI) is NOT necessarily what you get (in aphasia severity)".

Several studies have suggested that the extent of lesion size seen on CT or MRI is a predictor of aphasia severity (Kertesz, Harlock, & Coates, 1979; Mazzoni, et al., 1992, Pedersen, et al., 1995). There could be several reasons why the present results do not agree with these studies.

Because of technical limitations, these studies were not able to show the extent of hypoperfusion in stroke – something that was possible in the present study. In deed, the most likely explanation for the low correlation between aphasia severity and lesion size in the present study has to do with the presence of cerebral hypoperfusion. Given the high correlation between aphasia severity and hypoperfusion, it is probable that lesion size seen on DWI does not represent the extent of tissue that is functional in the acute-stage of stroke. None of the studies mentioned above looked at acute stroke, perhaps because T2-MRI and CT scans are not optimal techniques for lesion volume analyses in acute stroke. That is, using these techniques the ischemic lesion is often not observed until several days after the onset of stroke. PI and DWI overcome this limitation. The earliest time-point for examination was at one-month post-stroke by Mazzoni et al. (1992). Based on findings by Beaulieu et al. (1999), significant hypoperfusion beyond the actual lesion is not common in chronic subjects. Consequently, it is possible that hypoperfusion may be a confounding variable in the investigation of association between

lesion size and aphasia severity in acute stroke. That is, "what you see (on PI) is what you get (in aphasia severity)".

Another source for discrepancy between the present results and other studies may come from lack of statistical power because the present study used a smaller sample than the studies described above. Nine subjects were tested in the present study. A power analysis was performed to assess how many more subjects would have been needed to reveal a statistically significant correlation at an alpha level of .01. Using the correlation between BEST-2 scores and lesion size seen on DWI (-.22) as a reference effect size for the power analysis, a total of 103 subjects would be needed to reveal a significant correlation using an alpha level of .01 and power of .60. That is to say, if the same correlation between these two variables was found with increased sample size, 103 subjects would be needed for a statistically significant correlation.

Because PI provides information about tissue that is hypoperfused but not (yet) dead it is likely that PI more accurately reflects what cortical areas are receiving enough perfusion for neural firing than does DWI. Based on visual inspection, most subjects studied here appeared to have hypoperfusion that extended beyond the actual lesion. Consequently, left/whole brain perfusion ratio was a better predictor of aphasia severity than lesion size seen on DWI. Another advantage of PI is the capability to show the remote effects of stroke. EJ and CJ are both good examples of how lacunar infarcts can result in significant hypoperfusion beyond the actual lesions. EJ had two small infarcts but hypoperfusion that extended far beyond the actual lesion. It is possible that her conduction aphasia was not only a reflection of dead tissue in the lacunes but also of

hypoperfused tissue in the left parietal lobe. CJ's stroke was also very interesting in that much of her left hemisphere was hypoperfusied even though, just like EJ, she had only two lacunar infarcts. Moreover, CJ had global aphasia – something that would probably not be expected based on such small lesions.

Question 2

> Does aphasia severity correlate with cerebral hypoperfusion and lesion size seen on T2-MRI at thirty days post-onset?

The correlation between BEST-2 scores and hypoperfusion was not statistically significant at one month post-onset. That does not necessarily mean that perfusion in the left hemisphere at one-month post-stroke and aphasia severity are unrelated. Two important factors need to be considered here: Ceiling effect on the BEST-2 and statistical power. Unlike in the acute stage, when all subjects had at least mild aphasia as measured on the BEST-2, PH and LN scored within normal limits and JT[2] got all items correct on the BEST-2 at reassessment. Therefore, it is possible that the correlation is not statistically significant because of a ceiling effect on the language assessment. Thus, it is possible that PH, LN, and JT were still aphasic but that the BEST-2 was not sensitive enough to detect their aphasia. Indeed, PH and LN complained of having word finding difficulty at one-month post-stroke even though this difficulty was not apparent to the author. Even though the BEST-2 works well for assessment in acute care, other aphasia batteries that give more in-depth information may be used when subjects are able to

[2] The range for mild aphasia on the BEST-2 for persons under 75 years of age is 77-91. Even though JT had a perfect raw score it was not enough to place her performance within normal limits.

participate in longer diagnostic sessions. The BDAE has more subtests and items per subtest than the BEST-2. However, PH, LN, and JT did not make errors on the BDAE. The only language test on which errors occurred for these subjects at one-month post-onset was the Boston Naming Test (BNT). The variance of scores was greater on the BNT than on the BEST-2. Therefore, it is possible that the BNT reflected aphasia severity more accurately at this time than the BEST-2. Indeed, the correlation between BNT scores and hypoperfusion was statistically significant at the .01 level. Unequivocally, subjects who had low cerebral perfusion were more likely to score low on the BNT than subjects whose PI scans revealed more perfusion. ES and CJ had the lowest scores on the BNT. Both had significant hypoperfusion at one-month post-stroke. In contrast, PH who named 14 of 15 items correctly on the BNT did not appear to have hypoperfusion at one-month post-stroke. Even though PH did not make a single error on the BEST-2, BDAE, or informal language probes at one-month post-stoke she still had some residual language problems. Her friends reported that she was communicating as effectively as before the stroke but PH complained of occasional word finding difficulty – something that she did not experience before the stroke.

Statistical power needs to be considered when such a small sample has been studied. Using the correlation coefficient (.49) between BEST-2 scores and hypoperfusion as a reference effect size, a power analysis was carried out to estimate how many more subjects would be needed to reach statistical significance. Using an alpha level of .01, twenty subjects would be needed to attain power of at least .60. If a correlation of .49 is the true state of nature between BEST-2 scores and hypoperfusion, it

would suggest that there is relationship between aphasia severity and hypoperfusion at one-month post-onset, even though it may not be as strong as in the acute stage. It is likely that decreased cerebral perfusion at one-month post-stroke is associated with more severe aphasia. This seems to be an obvious observation but it is one that needs to be stated because researchers who use lesion data to investigate language function usually assume that what is seen on T2-MRI represents brain tissue with neurons that are capable of firing. T2-MRI does not reveal the remote effects of stroke, something that needs to be taken into account in studies of brain-language relationships. The existence of cerebral hypoperfusion in chronic stroke may also have important implications for treatment of stroke. It has been suggested that more detailed blood pressure management in cases of low cerebral perfusion in stroke may aid in reducing the ischemic penumbra after the three-hour time-window for tPA therapy.

The correlation coefficient between BEST-2 scores and lesion size seen on T2-MRI was statistically significant at an alpha-level of .05. Power analysis revealed that with a correlation of -.75, power of .60 would have been reached with nine subjects for an alpha level of .01. Thus, if the correlations found in this sample were to hold true in the population, there would appear to be a stronger relationship between aphasia severity and lesion size at one-month post-stroke than in the acute stage.

At one-month post-stroke perfusion images of the brains of PH and LN appeared to reveal normal perfusion. Compared to day one, perfusion was also increased in the left hemispheres of CJ and RI. Therefore, it is probable that perfusion had less an effect on the relationship between lesion size and aphasia severity at this time.

Secondary Question 1

> Does aphasia severity have higher correlation with hypoperfusion and lesion size seen on DWI than face discrimination ability within 24 hours of symptom onset?

There was much greater variation in subjects' performance on the BEST-2 than on the FAB. The fact that BEST-2 scores had higher correlations with hypoperfusion and lesion size than FAB scores suggests that subjects' performance on the BEST-2 was a reflection of aphasia severity rather than some other factor such as decreased attention. Case in point, EM, who had the lowest BEST-2 score immediately post-stroke but only missed one item on the FAB. CJ received the lowest score on the FAB (13/20) and the second lowest score on the BEST-2. It is possible that right homonymous hemianopsia could have contributed to her performance on the FAB.

Other evidence also supports the notion that subjects' aphasia severity was reflected on the BEST-2 instead of decreased attention. All subjects in this study were diagnosed by the attending neurologist as having aphasia. None, however, were noted to have decreased arousal or difficulty attending during the neurological exam.

Secondary Question 2

> Does aphasia severity have higher correlation with hypoperfusion and lesion size seen on T2-MRI than face discrimination ability at one-month post-onset?

As in acute care, the correlation between BEST-2 scores and hypoperfusion was higher than the correlation between FAB scores and hypoperfusion. This was also true

for the relationship between behavioral data and lesion size seen on T2-MRI. At this time, no subjects appeared to have difficulty attending to the language test. Therefore, the issue of decreased attention influencing performance on language tests was not as important as in the acute stage of stroke. In fact, six of seven subjects had experienced significant recovery from aphasia and had resumed their pre-stroke lifestyles and activities. The only subject who got worse on the FAB and the BEST-2 was ES. She was also the only subject whose perfusion appeared to have decreased on the follow-up scan. It was obvious that her aphasia was increasing in severity at this time. She was making more phonemic paraphasias in running speech and was having increased difficulty with auditory comprehension. It is possible that the global decrease in perfusion not only affected her language but also other aspects of cognition such as attention.

NIHSS – Perfusion and Lesion Size

NIHSS scores did not have a statistically significant correlation with hypoperfusion or lesion size immediately post-stroke. These results do not agree with other studies (Beaulieu, et al., 1999; Chalela, et al., 2000; Lev, et al., 2001; Neumann-Haefelin, et al., 1999; Tong, et al., 1998). It is probable that the difference stems from more careful subject selection in the present study. The studies mentioned above all investigated subjects with various neurological impairments. The present study only included subjects with aphasia and excluded those who possibly had aphasia but were not able to participate in behavioral testing in acute care. Therefore, the range of possible

NIHSS scores was reduced simply because only aphasic persons whose aphasia was not confounded by more complex cognitive problems and poor neurological status served as subjects here.

Language is measured on the NIHSS using a 4-point rating scale. Therefore, the range of scores for aphasia severity rating is small. Consequently, a subject like EF who had severe aphasia only received an NIHSS score of 4 (1 point for homonymous hemianopsia) despite a very large cortical lesion and extensive hypoperfusion (a score of 4 on the NIHSS is not even high enough to qualify for tPA treatment). Therefore, because the focus of the present study was aphasia (but not overall neurological status) the BEST-2 was a much better indicator of stroke related deficits than the NIHSS for the subjects investigated here.

The correlation between NIHSS scores and hypoperfusion was not statistically significant at one-month post-stroke. It did, however, reach statistical significance for the relationship between NIHSS scores and lesion size. As with scores on the FAB and one-month post-stroke, the variance of NIHSS scores was very limited with a restricted range (0-6) placing little significance on these results.

Recovery – Fluent Aphasias (N = 6)

Most subjects in this study were followed throughout the month following their stroke either through home visits or phone calls. In addition, RI and ES were also contacted after the one-month period post-stroke for more follow-up information. The

following are reports of how subjects with fluent aphasia recovered in the weeks and, sometimes, months following stroke.

Three subjects (EJ, JT, and ES) had conduction aphasia in the acute stage. All three made frequent phonemic paraphasias both in connected speech and while repeating words and phrases.

EJ had the lowest score of these three on the BEST-2 in acute care. Even though EJ experienced significant recovery from aphasia (her BEST-2 score went from 67 in the acute stage to 84 at one-month post-stroke), she still made significant number of phonemic paraphasias in running speech and she also had difficulty with repetition and auditory comprehension at one-month post-stroke. Because EJ declined to be rescanned it is impossible to determine whether a change in cerebral perfusion or lesion size would have been observed. However, she had been undergoing aggressive chemotherapy for cervical cancer during the month following her stroke, which certainly could have confounded this picture. In a review article, Olin (2001) reported significant decline in memory, attention, and language function in breast-cancer patients undergoing chemotherapy. Even though EJ experienced significant recovery from aphasia, it is possible that the chemotherapy had an effect on the extent of recovery.

JT was the only subject with conduction aphasia in the acute stage who experienced complete recovery. What also distinguishes JT from other subjects in the study is the fact that no lesion was noted in her brain on the DWI or T2-MRI. She did, however, have stroke like symptoms in acute care that persisted for at least 48 hours. These symptoms were accompanied by bilateral hypoperfusion. Visual inspection of

JT's PI scan at one-month post-onset, suggested that perfusion had increased compared to acute stage. In a study of 27 subjects with stroke like-deficits without an apparent lesion seen on DWI, Ay et al. (1999) speculated that a decrease in cerebral perfusion may halt neural firing but that these areas may reperfuse without cerebral ischemia. It is impossible to determine if this was the case with JT. No seizure activity was noted on an electro encephalogram (EEG) and symptoms persisted beyond the time course typical of a TIA. Other studies that have investigated perfusion and diffusion in stroke have also included subjects with hypoperfusion deficits without a lesion seen on the DWI (Neumann-Haefelin, 2000; Tong et al., 1998).

ES was the only reexamined subject in the study who did not show at least partial recovery from aphasia. She was also the only subject whose PI showed a decline in perfusion compared to the acute stage. This perfusion decline was accompanied with significant increase in aphasia severity. At one month post-stroke, the number of phonemic paraphasias was significantly increased in running speech and she had severe difficulty with repeating even single words. In addition, auditory comprehension was now impaired. ES had another left hemisphere stroke one-month following her participation in this study that resulted in even more severe aphasia. It is tempting to speculate that the cognitive and hemodynamic deterioration of ES was a precursor of her latest stroke. There is no data, however, to support that decreased perfusion is a significant predictor of stroke recurrence.

Two subjects (RI and LN) had anomic aphasia in the acute stage. Both experienced significant aphasia recovery. RI still had mild anomic aphasia and agraphia

at one-month post-stroke. Even though his PI showed increased perfusion on reexamination, RI's scan still showed hypoperfusion beyong the area of the actual lesion, as seen on T2-MRI. At three months post-stroke, RI reported that he did not have any difficulty writing and that he was again corresponding with friends around the country.

RI was the only subject in the study who was treated with tPA. Even though he experienced significant recovery from aphasia, other subjects also recovered as well as he did. Interestingly, his cortical lesion decreased in size from the acute stage to one-month post-stroke. In a recent study of lesion size evolution seen on DWI and T2-MRI, Lansberg, O'Brien, Tong, Moseley, and Albers (2001) suggested that resolution of edema and decrease in inflammatory infiltration probably contribute to decrease in lesion volume between 4 and 25 days post-stroke. They did not specify, however, whether their subjects were treated with thrombolytic agents. RI was very busy traveling in the months following his stroke and did not have time for a third examination. It would have been interesting, for example, to see his PI and T2-MRI scans at three-months post-stroke when he reported that he was free from language problems.

LN, who had only mild aphasia to start with, scored within normal limits on the BEST-2 on the reassessment. At this time, she only experienced occasional word finding problems. Even though the T2-MRI showed a lesion at one-month post-stroke, there was a significant improvement in perfusion.

One subject – EF – had Wernicke's aphasia. He probably had a stenosis of the left internal carotid artery that led to a large anterior-posterior cerebral lesion with significant hypoperfusion. Even though EF was not examined again, his wife reported

that he was "making much more sense" the week before he had the second stroke (27 days after the initial stroke). It was not possible to follow EF after he left the hospital, due to the increased household responsibilities that had fallen to his wife since EF's stroke. Ms. EF reported that she was overwhelmed and did not want to be "bothered with what was not medically necessary". She did, however, agree to bring him to the hospital for follow up testing and MRI. This never took place because of EF's second stroke and subsequent death at one-month after his first stroke.

Recovery – Non-Fluent Aphasias (N = 3)

All three subjects (CJ, MG, and PH) who had non-fluent aphasia experienced substantial recovery from aphasia during the month after onset. The following paragraphs describe recovery for each of these subjects. CJ and PH came back for reexamination at one-month post-stroke and CJ's sister was contacted at two-months after inclusion in the study for more follow-up information.

CJ was the only subject in the study who initially had global aphasia. She experienced substantial recovery from aphasia during the month following stroke. She also demonstrated significant improvement in left hemisphere perfusion at the time of reexamination. Even though her fluency had improved, her speech consisted primarily of the use of short, but grammatically-correct, phrases. At two months following stroke, her sister reported that CJ's communication ability had not changed much compared to one-month post-stroke.

MG experienced extensive aphasia recovery during hospitalization. At day one, she had severe Broca's aphasia. The following day she was able to name 5 out of 5 objects correctly, repeat 5 single words and 3 out of 5 phrases. She could also speak in short sentences and even spoke to her sister on the phone. Occasional paraphasias were noted in running speech and a few sentences were agrammatical. A conversation with MG's sister at two weeks after discharge from the hospital revealed that MG was not "talking as much as before" and that she was not going back to work. At one-month post-stroke MG's sister was contacted again to request a follow-up examination for MG at UMC. Regrettably, MG declined reexamination because she lived five hours from UMC. MG did not have a phone in her house. Therefore, it was not possible to get a language sample this time. Her sister reported that MG's ability to communicate had not changed since the conversation at two-weeks post-stroke.

PH was one of only two subjects in the study who scored within normal limits on the BEST-2 at one-month post-stroke (the other was LN). Compared to other subjects, PH's perfusion-scan showed very little hypoperfusion in the acute stage. It is not clear if this was a factor in her significant recovery. Schwamm et al. (1998) found that mismatch between the actual lesion seen on DWI and hypoperfusion seen on PI was a significant predictor of neurological recovery measured on the NIHSS. They suggested that a lesion surrounded with a large ischemic penumbra was more likely to increase in size than a lesion of similar size without surrounding hypoperfusion. Moreover, a large ischemic penumbra was found to be predictor of poorer neurological outcome than when a lesion of similar size was not surrounded by hypoperfusion. Therefore, it is possible that the

small lesion seen on the DWI scan for PH did not increase in size because of adequate surrounding perfusion.

At one-month post-stroke, PH was back to her old routine of visiting friends, going to social events, and traveling. In fact, the week prior to her reexamination she went with her granddaughter on a five day cruise to Alaska. She was very interested in the results of the present study and requested a copy of the article.

Implications

As discussed earlier, few investigations of factors involved in spontaneous recovery from aphasia have focused on hemodynamic changes following stroke (Cappa et al. 1997; Mazzoni, et al., 1992; Thulborn, Carpenter, & Just, 1997) and none of these studies have looked at aphasia in the acute stage. The present study suggests that changes in perfusion and lesion size immediately following stroke play important roles in early recovery from aphasia. That is, as perfusion increases in and around cortical language areas, aphasia severity appears to decrease.

Five of the six subjects who received behavioral testing and MR imaging in acute care and again at one-month post-stroke experienced significant recovery from aphasia. This recovery was accompanied – in all cases – with improvement in cerebral perfusion. If further studies support that this is the case in the general population of acute stroke patients, speech-language pathologists (SLPs) might do well to consider delaying therapy until changes in cerebral perfusion cease. If perilesional areas are hypoperfused to the point that neurons in these areas cannot fire, it seems futile to focus therapy on language

processes that rely on these same areas. It appears more appropriate to postpone language treatment until after perilesional areas have gained adequate perfusion for neural firing. The notion of delaying treatment based on neurophysiological factors is perhaps further supported by Schallert, Kozlowski, Humm, and Cocke (1997), who suggested that increased cortical stimulation of the lesioned rat-brain in the first 10-14 days following onset leads to increase in lesion size and cessation of dendritic growth in the perilesional area. It is not clear if there is a direct link between this work and aphasia treatment but the idea is intriguing.

Future Research

Further research related to the topic of the present investigation should seek to increase the sample size, as well as to consider in more detail how changes in perfusion and lesion size may affect aphasia outcome. For example, it would be interesting to study how the mismatch between the actual lesion size and hypoperfusion in the acute stage may affect recovery from aphasia. That is, does a patient who has a large ischemic penumbra (e.g. LN) recover more or less than someone who does not have hypoperfusion beyond the actual lesion seen on DWI (PH). Further, the effect of preventative factors such as tPA treatment and administration of neuroprotective agents could be investigated, as was suggested in the case of RI.

From the standpoint of neuroimaging, it would be helpful to look at ways to increase brain coverage of the PI technique. For example, brain perfusion images of normal subjects could be compared using between five and eight slices with different

times (TI) between image labeling and image acquisition. Increased PI coverage could make it possible to estimate volume of cerebral hypoperfusion in addition to a left/whole brain perfusion ratio.

Final Note

Although the purpose of this study was not to investigate the role of the SLP in aphasia management in acute stroke, the study provided important insights regarding this matter. The author probably spent more time with the aphasic subjects and their families in acute care than any other members of the medical team. This time was spent gathering data through formal and informal testing as well as providing counseling. Even though nursing staff and doctors provided personal support and care, they simply did not – because of the nature of their jobs – have as much time to spend with patients and families as the investigator. By providing counseling in acute care, the investigator was able to establish a good report that lasted well beyond acute care. For example, six of the nine subjects requested speech therapy from the investigator even though some of them were already being treated on outpatient basis.

Of course this does not suggest that staff SLPs need to spend several hours per day with patients in acute care as was the case in this study. It does, however, suggest that instead of spending an hour on formal assessment in one day, it may be more beneficial for patients with aphasia and their families to be seen in three 20 minute sessions per day where sessions would focus on short informal assessments and

counseling. This would provide care that is typically not provided by other members of the medical team and set the tone for later aphasia treatment.

Summary

In the present study, aphasia severity was found to correlate with hypoperfusion immediately post-stroke and at one-month post-stroke. Furthermore, five of six subjects who experienced at least partial recovery from aphasia appeared to have increased cerebral perfusion at one-month post-stroke. Lesion size was a significant predictor of aphasia severity at one-month post-stroke but not in the acute stage.

These results suggest that changes in perfusion may contribute to spontaneous recovery from aphasia following stroke. Furthermore, the relationship between aphasia severity/type and lesion size may be influenced by the presence of cerebral hypoperfusion. This study suggests that changes in perfusion and lesion size may be used to predict early aphasia recovery following stroke.

Appendix A.

CORRELATIONS FROM BEAULIEU ET AL., 1999

	NIHSS (day 1)	NIHSS (day 30)
Hypoperfusion – day 1	.73 (.0006)	.84 (.0001)
Hypodiffusion - day 1	.55 (.0100)	.86 (.0001)
Max volume* - day 1	.91 (.0001)	
Hypodiffusion - day 30		.85 (.0001)

*Maximum volume observed on either PI or DWI

Appendix B.

LANGUAGE TEST – BEST-2

Table 1. Summary of BEST-2 scores for EF

	Day 1		
BEST-2	Raw sc	Stn. sc	Sev. Rat
Conversational Expression	2	6	Sev
Naming objects	0	5	"
Describing objects	0	5	"
Repeating Sentences	0	5	"
Pointing to objects	0	4	"
Pointing to parts of a pix	0	5	"
Reading	0	6	"
Total		36	"

Table 2. Summary of BEST-2 scores for CJ

	Day 1			Day 30		
BEST-2	Raw sc	Stn. Sc	Sev. rat	Raw sc	Stn. sc	Sev. rat
Conversational Expression	0	6	Sev	16	7	sev
Naming objects	2	6	"	24	10	mod
Describing objects	5	7	"	24	8	sev
Repeating Sentences	12	7	"	30	13	mild
Pointing to objects	11	7	"	26	9	mod
Pointing to parts of a pix	4	6	"	24	8	sev
Reading	0	6	"	8	8	sev
Total		45	"		63	mod

Table 3. Summary of BEST-2 scores for MG

	Day 1		
BEST-2	Raw sc	Stn. Sc	Sev. Rat
Conversational Expression	6	6	Sev
Naming objects	12	7	"
Describing objects	8	7	"
Repeating Sentences	6	6	"
Pointing to objects	24	9	Mod
Pointing to parts of a pix	30	13	no imp
Reading	6	8	"
Total		56	Sev

Table 4. Summary of BEST-2 scores for RI

	Day 1			Day 30		
BEST-2	Raw sc	Stn. Sc	Sev. rat	Raw sc	Stn. sc	Sev. rat
Conversational Expression	22	9	mod	27	10	no imp
Naming objects	13	9	mod	30	13	Mild
Describing objects	9	8	sev	28	12	Mild
Repeating Sentences	29	11	mild	30	12	Mild
Pointing to objects	3	6	sev	30	14	no imp
Pointing to parts of a pix	26	11	mild	26	11	Mild
Reading	20	11	mild	18	10	Mod
Total		65	mod		82	Mild

Table 5. Summary of BEST-2 scores for EJ

	Day 1			Day 30		
BEST-2	Raw sc	Stn. sc	Sev. rat	Raw sc	Stn. sc	Sev. rat
Conversational Expression	27	9	mod	29	11	mild
Naming objects	27	10	mod	28	11	mild
Describing objects	26	10	mod	30	14	wnl
Repeating Sentences	28	10	mod	30	12	mild
Pointing to objects	27	9	mod	30	13	wnl
Pointing to parts of a pix	28	11	mild	30	13	wnl
Reading	10	8	sev	18	10	mod
Total		67	mod		84	mild

Table 6. Summary of BEST-2 scores for JT

	Day 1			Day 30		
BEST-2	Raw sc	Stn. sc	Sev. Rat	Raw sc	Stn. sc	Sev. rat
Conversational Expression	26	9	Mod	30	12	Mild
Naming objects	28	11	Mild	30	13	No imp
Describing objects	24	10	Mod	30	14	"
Repeating Sentences	30	12	Mild	30	12	Mild
Pointing to objects	26	9	Mod	30	13	No imp
Pointing to parts of a pix	24	8	Sev	30	13	"
Reading	18	10	Mod	30	14	"
Total		69	Mod	24	91	Mild

Table 7. Summary of BEST-2 scores for PH

	Day 1			Day 30		
BEST-2	Raw sc	Stn. sc	Sev. rat	Raw sc	Stn. Sc	Sev. rat
Conversational Expression	16	8	sev	30	13	No imp
Naming objects	11	8	sev	28	13	"
Describing objects	12	8	sev	30	14	"
Repeating Sentences	26	10	mod	30	12	"
Pointing to objects	30	14	no imp	28	14	"
Pointing to parts of a pix	26	11	mild	30	14	"
Reading	30	15	no imp	24	13	"
Total		74	mild		93	"

Table 8. Summary of BEST-2 scores for LN

	Day 1			Day 30		
BEST-2	Raw sc	Stn. Sc	Sev. rat	Raw sc	Stn. Sc	Sev. rat
Conversational Expression	22	8	sev	30	13	no imp
Naming objects	30	13	no imp	30	13	"
Describing objects	24	11	mild	30	14	"
Repeating Sentences	26	10	mod	30	12	"
Pointing to objects	21	10	mod	30	14	"
Pointing to parts of a pix	30	14	no imp	30	14	"
Reading	16	10	mod	24	13	"
Total		76	mild		93	"

Table 9. Summary of BEST-2 scores for ES

	Day 1			Day 30		
BEST-2	Raw sc	Stn. Sc	Sev. rat	Raw sc	Stn. Sc	Sev. rat
Conversational Expression	24	9	mod	16	7	Sev
Naming objects	24	9	"	16	8	"
Describing objects	24	10	"	30	14	no imp
Repeating Sentences	21	8	sev	19	8	Sev
Pointing to objects	30	13	no imp	28	11	Mild
Pointing to parts of a pix	30	13	"	25	9	Sev
Reading	30	14	"	12	8	Sev
Total		76	mod		65	Mod

Appendix C.

CASE REPORTS

EF

EF was a 77 year-old Caucasian man who had been retired as an air conditioning repairman for 16 years. He lived with his wife in Tucson during the winter months but in Michigan during the summers. During the hour prior to admission, he was involved in a couple of minor accidents while driving his car. The neurological exam revealed acute stroke with aphasia and right homonymous hemianopsia.

Of the subjects who participated in this study, EF had the most severe aphasia immediately post stroke. His performance on the BEST-2 revealed severe Wernicke's aphasia. Verbal expression was characterized by neologisms and single syllable repetitions. EF did not appear to be aware of his language problem. His affect was pleasant and he eagerly participated in the testing.

The DWI showed a large left hemisphere stroke, affecting both anterior and posterior distribution of the MCA. Significant left hemisphere hypoperfusion was revealed by the PI scan – extending beyond the lesions seen on DWI.

Four weeks after this first stroke he suffered another stroke. This second stroke affected the brainstem and cerebellum and resulted in extensive neurological deficits. EF died two days after this stroke.

CJ

CJ is a 77 year-old Mexican-American woman who has been living with her sister since her husband died nine years ago. She is a mother of seven children and spends much of her time with them and her grandchildren. Her first language is Spanish but since marrying her American husband, she has mainly communicated in English. Her daughter explained that Spanish was rarely spoken in their household and that none of CJ's children speak Spanish.

CJ's history included hypertension, diabetes, smoking, and a right hemisphere stroke that resulted in transient dysarthria in 1995. Symptoms associated with her current stroke were first noticed by her son at 10 o'clock in the morning. She was not brought to the emergency room until in the evening of that same day. On admission, the neurological exam revealed global aphasia, right facial droop, right homonymous hemianopsia, and unsteady gait. The DWI showed two left hemisphere lacunar infarcts, one of which was subcortical and one in the left parietal lobe. The PI revealed hypoperfusion involving much of the left hemisphere.

CJ was the only subject in the study who was diagnosed as having global aphasia. Consistent with the resident neurologist's assessment from the previous day, CJ's performance on the BEST-2 was poor. For example, on the Conversational Expression subtest she responded to most items with "I don't know". The only subtest on which she scored at least one point on each test item was "Repeating Sentences," where she was able to repeat two simple phrases and three single words. CJ was scanned and tested again at one month post-stroke. Her sister stated that even though the subject still had

trouble communicating she was "pretty much back to her old routine" of visiting children and grandchildren. Her standard score on the BEST-2 increased from 45 to 63. At the time of the second test, her speech consisted of 3-4 word utterances. She was also able to read some short sentences out loud. Her auditory comprehension was also much improved. She could now follow simple two-step commands and answer biographical questions with good accuracy.

Compared to day one, left hemisphere perfusion was increased at one month post-onset. However, the actual lesion size appeared to have increased. The T2-MRI shows significant hypodensity in the left parietal lobe.

CJ was tested with the BDAE at one-month post-stroke. Her performance on the BDAE largely reflected the results from the BEST-2 – anomia, mostly short sentences, minor problems with auditory comprehension, and severe alexia/agraphia.

On the BNT, CJ was able to name four of the fifteen items correctly. Following a phonemic cue, she named 3 of the 11 missed items correctly.

An informal language probe was administered in Spanish at day 11 by a second investigator. Her language proficiency in Spanish was poorer than in English. The subject's sister reported that her Spanish seemed more affected by the stroke than English.

MG

MG is a 70 year-old American Indian woman who used to work cleaning houses. She lives on the White River reservation with her partner and brother. MG was admitted to the hospital with congestive heart failure. Two days after admission, nurses noted that she was having difficulty speaking. The admitting physician requested consultation from Neurology. The neurological exam revealed non-fluent aphasia accompanied by flaccid dysarthria.

MG's performance on the BEST-2 indicated severe aphasia. Even though her auditory comprehension appeared to be intact, her verbal expression was so limited (occasional single words) that she only received 32 points out of 90 possible on the first three parts of the BEST-2. She was able to name two of five pictures and repeat two out of five single words correctly. MG frequently uttered stereotypes such as "pah" in conversation.

The DWI showed a cortical lesion in the left posterior-medial frontal lobe. There appeared to be significant hypoperfusion in the left hemisphere.

MG was discharged from the hospital 4 days after the onset of stroke. Her sister was contacted about bringing MG back in one-month. Due to the long distance from their residence to the hospital, they opted not to come back for reassessment.

RI

RI is a 79 year-old retired college professor who lives with his wife in a retirement community. He was brought to the hospital with acute stroke accompanied by "slurred and confused speech". The neurological exam revealed intact cranial nerves and an acute onset of aphasia. The MRI showed a left MCA stroke involving the frontal lobe, including Broca's area.

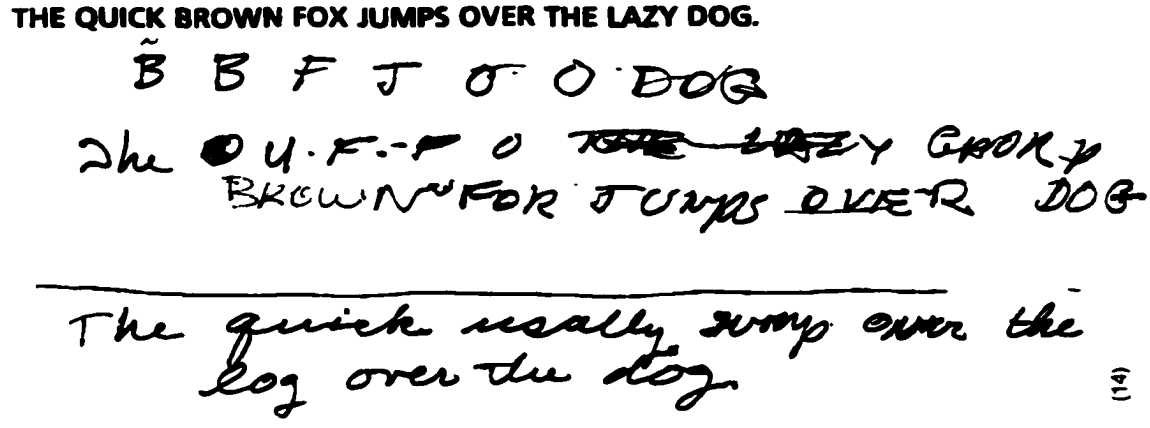
Based on the rating scale of aphasia severity on the BEST-2, RI had moderately severe aphasia that was characterized mainly by anomia. He also had difficulty with identifying pictures of objects in a field of 16 items. However, expression in conversation was only moderately impaired and was mainly affected by frequent word finding difficulty, semantic paraphasias, and occasional perseverations.

On re-examination at one month post-stroke, RI had only mild anomia. Paraphasias and perseverations were absent. When he had word finding difficulty he usually remarked that "It will come back to me" or "if I just slow down, I can say it". His standard score on the BEST-2 improved from 65 to 82.

At second testing, the T2-MRI scan showed hypodensity in the area of the acute stroke. There appeared, however, to be an increase in perfusion around the lesion compared to day one.

RI was administered the BDAE at two days following the second MRI session. His performance suggested minimal difficulty in auditory comprehension, oral expression and reading. He did, however, have significant writing difficulty reflected in a word-length effect and in copying written sentences (Figure 8).

Figure 8. Copy of a sentence from the BDAE by RI (print and cursive copy)



On the short form of the BNT, the subject named eleven of fifteen pictures correctly. All errors consisted of semantic paraphasias such as "Egypt" for "Sphynx" and "Ship" for "Canoe."

EJ

EJ is a 74 year-old retired secretary who had been admitted to UMC for cervical cancer treatment when she suffered a stroke. She has a medical history of cancer, mastectomy, atrial fibrillation, and sudden weight gain (9 pounds) during the week before inclusion in the study. EJ was referred to Neurology at 4:00 p.m. and tested and scanned the following day between one and three in the afternoon. Her MRI session took over two hours due to the high number of scans needed of the brain and thorax. The DWI scan revealed two lacunar infarcts, one sub-cortical and one in the left posterior parietal lobe. There was marked hypoperfusion in the left posterior parietal lobe.

EJ's aphasia was characterized by frequent phonemic paraphasias that caused her much anxiety. Based on EJ's standard score on the BEST-2 she had moderately severe aphasia immediately post-stroke. Her test performance was characterized by intermittent phonemic paraphasias especially while reading sentences. Phonemic paraphasias were much greater in conversational speech than on individual subtests of the BEST-2.

Citing claustrophobia, EJ refused to have an MRI at one-month post-stroke. She did agree, however, to go through with the language tests. The BEST-2, FAB, and BDAE were administered in two sessions while EJ was receiving chemotherapy at the UMC Cancer Center. Compared to day one, she improved from moderate to mild aphasia. Paraphasic errors were noted on reading aloud. Despite scoring within normal limits on some subtests (Repeating Sentences, Describing Objects, & Pointing to Objects), she made 1-2 phonemic paraphasic errors per sentence in conversation.

The BDAE was administered one week after the BEST-2. EJ still produced intermittent phonemic paraphasias in conversation and while repeating sentences. Her husband noted that numbers "give her a lot of trouble". She was unable to tell time and had acalculia. On the BNT, EJ scored 12/15. Two of the initially incorrectly named items were named when a phonemic cue was provided.

JT

JT is a 70 year-old Caucasian woman who lives with her husband in a retirement community. She was vice president of a bank prior to her retirement 6 years ago. Prior to the admission she had had two transient ischemic attacks. She has a history of lung cancer and heart bypass surgery in 2000. Her husband reported that early in the morning of her admission JT had awakened feeling "agitated". Her husband reported that her speech "made little sense" at that time, and was immediately transported to the hospital. The neurological exam revealed intact cranial nerves but aphasia that was characterized by frequent phonemic paraphasias. Her MRI did not show a lesion on DWI. However, the PI revealed what appeared to be bilateral hypoperfusion.

Her total standard score on the BEST-2 was 69 which indicates moderately severe aphasia. Phonemic paraphasias were evident in conversation. For example, attempting to describe her previous career, she said "bandleader, no, no, no" but was able to say "banker" when given a carrier phrase.

JT was scanned at one-month post-onset and also underwent language testing at that time. She made no errors on the BEST-2 and appeared to have no residual language problems. Her BDAE performance was perfect. She corrected her two errors on the BNT when provided with a phonemic cue.

No lesion was apparent on the neither the DWI or T2-MRI. Compared to the PI in acute care, there appeared to an increase in global perfusion at one-month post-onset of symptoms.

PH

PH is a 79 year-old retired math teacher who lives alone but has a very active life. One-hour prior to her admission to the hospital, her neighbour came over for a morning visit and noted she was having difficulty speaking. The neurological exam revealed non-fluent aphasia without any other significant findings and an NIHSS score of two. PH has a history of hypertension.

The results from the BEST-2 indicated mild aphasia characterized by limited verbal output, severe anomia, but intact ability to read (silently), write, and repeat sentences. On the Naming subtest, she was able to name all five pictures correctly when a phonemic cue was provided. She was able to answer all questions correctly following silent reading of a paragraph, but she was unable to read out loud. Much like MG, PH performed well on the Best-2's auditory comprehension sub-tests.

The DWI showed a left frontal lobe lesion superior to Broca's area. The PI showed perfusion abnormality in the area of the actual lesion but an ischemic penumbra was not noticed. In fact, consulting the DWI and PI scans, the managing neurologist and radiologist decided not to administer tPA.

PH was examined again at one month post-stroke. By this time, she had made significant recovery and did not appear to have aphasia. She complained, however, that she was not back to her "old self" and that she sometimes had difficulty with finding the right words. Moreover, she had given up on reading a "challenging" book because of difficulty with remembering what she had read previously. Her standard score on the BEST-2 was 93, within the normal range.

The cortical lesion was still apparent on T2-MRI. Hypoperfusion, however, was not visible on the PI scan.

Testing with the BDAE was carried out at the hospital two days after the second MRI session. She got all the items on the BDAE correct and only missed one item on the BNT.

LN

LN is a 76 year-old Caucasian woman who has been living by herself since fall, 2000 when her husband died. A retired secretary, she has two daughters who spend a lot of time with her. On the day of her stroke she awakened from an afternoon nap feeling ill. Her daughter called her shortly after LN woke up and noticed that her mother was not "talking right". She was brought to the hospital later that day. The neurological exam revealed "expressive aphasia" and right facial and arm weakness. The MRI showed a left hemisphere stroke affecting the insula and parietal lobe. The PI showed hypoperfusion extending beyond the lesions seen on DWI.

Language testing followed the MRI session. The sum of standard scores was 76, indicating mild aphasia as measured by the BEST-2. Her conversational expression was marked by word retrieval difficulty and what seemed to be unrelated paraphasias. She was highly aware of her errors. For example, when asked how old she was she responded "twenty, no one-hundred, no hundred and six, no I'm messed up, I can't believe I can't say my age". Her paraphasic errors were even more apparent when she was reading aloud

In addition to having problems with expression and reading LN also had significant agraphia. At day two, when asked to write her name she wrote (in cursive) "T-h-u-r-s-i-y a-d-l-o-a-y" and address "T-i-s-o-n-y S-h-a b-u-r-y". She wrote "star" correctly. At day three the subject was able to sign her name correctly but for her address she wrote (in cursive) "s-t-a-t-c-h". She could not copy single words. For instance, she

wrote in cursive "C-t-a-l-i-f-n-a C-a-t-a-d-n-y". for CALIFORNIA (print) and "P-a-t-t-i-n" for STAR (print).

LN was tested and scanned again at one month post-stroke. At this time, she appeared to have mostly recovered from the aphasia and she reported only having occasional problems with "remembering the words that I want to say". She scored within normal limits on all of the BEST-2 subtests and made no errors on the BDAE. She scored 10/15 on the BNT, but all items were correctly retrieved following a phonemic cue. Agraphia was gone, she wrote a detailed and accurate description of a picture from the BDAE and made no errors copying.

Visual inspection of T2-MRI images suggested that the lesion size was similar to what was seen on DWI in acute care. Perfusion, however, had improved greatly compared to the initial scan.

ES

ES is a 70 year-old woman who lives with her son. She previously worked as a nursing aide but retired 5 years ago. She is a mother of seven children and spends most of her time watching television or meditating. Her medical history is significant for hypertension, triple heart bypass surgery in the fall of 2000, and a right parietal lobe stroke in 1999. ES was brought to the hospital by her son who reported that she was having difficulty "saying things". ES was seen by a Neurology-resident who reported no significant findings beyond "expressive aphasia". She had an MRI the following morning. The DWI scan showed cortical lesions involving the left frontal and parietal lobes. The PI revealed hypoperfusion that extended beyond the borders of the lesions seen on DWI.

The BEST-2 was administered immediately following the MRI session. Conversational expression was marked by frequent phonemic paraphasias. For example, when trying to name BUTTON she said "puki no kuni no,no,no,...buki". At this time, ES was very labile and often laughed uncontrollably at her paraphasias. She had difficulty with repetition making 1-2 phonemic paraphasias per sentence.

ES was re-examined at one month post-stroke. At that time, her aphasia had worsened. Phonemic paraphasias and perseverations were more noticeable than before and auditory comprehension and reading ability were now impaired. The T2-MRI revealed that the lesion size had increased considerably compared to day one. Also, the PI showed a striking decrease in global perfusion. ES's neurologist was notified immediately of this change. He suggested that perhaps she was taking too much

medication for hypertension. Subsequently, her dose was decreased to try to increase cerebral perfusion.

She was not tested with the BDAE until five days after her second MRI scanning session. Her performance on the BDAE was even more impaired than the BEST-2 the previous week might have predicted. Phonemic paraphasias were present in almost every sentence. Her granddaughter reported that ES's aphasia varied considerably from one day to the next and that this was a particularly difficult day. She named 6 of the 15 pictures on the BNT correctly.

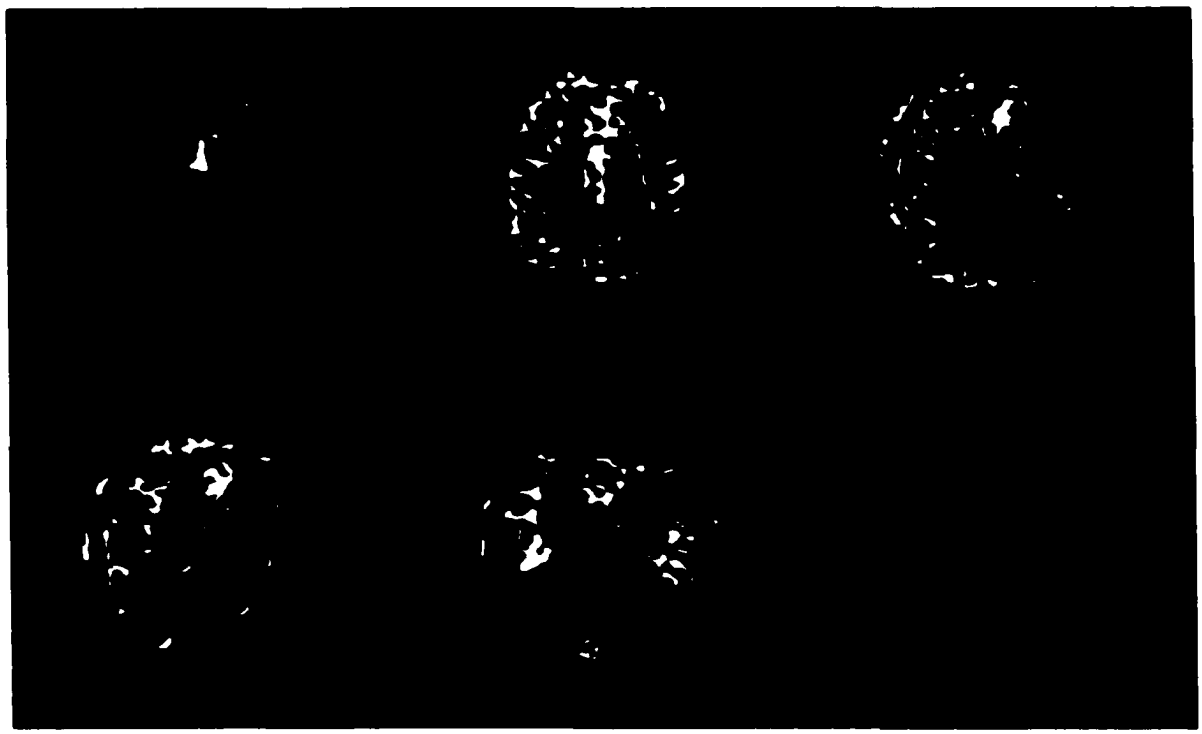
Three-weeks after the last testing session ES had another left hemisphere stroke that left her with even more severe aphasia. According to her son her aphasia has lessened but her ability to communicate varies from day to day.

Appendix D.

PATIENT IMAGES

Figure 1. EF (acute stage)

Perfusion Images



DWI

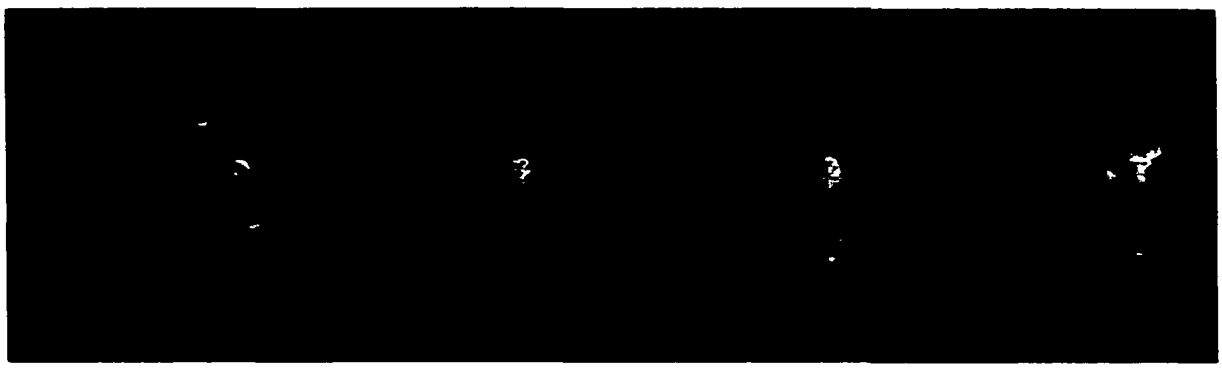


Figure 2. CJ (acute stage)

Perfusion Images

DWI

Figure 3. CJ (one-month post-stroke)

Perfusion Images

T2-MRI

Figure 4. MG (acute stage)

Perfusion Images

DWI

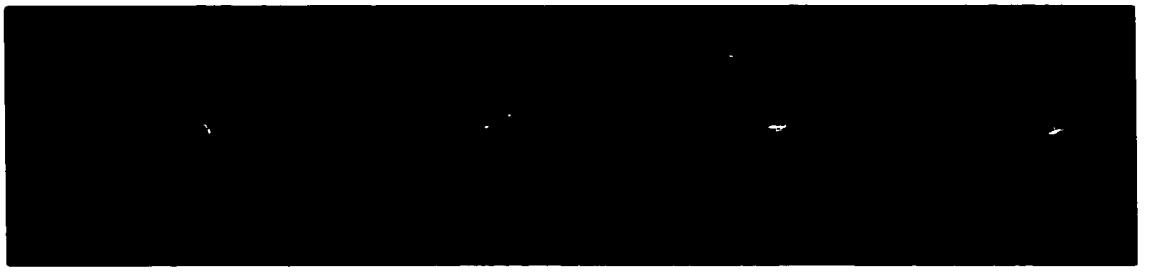
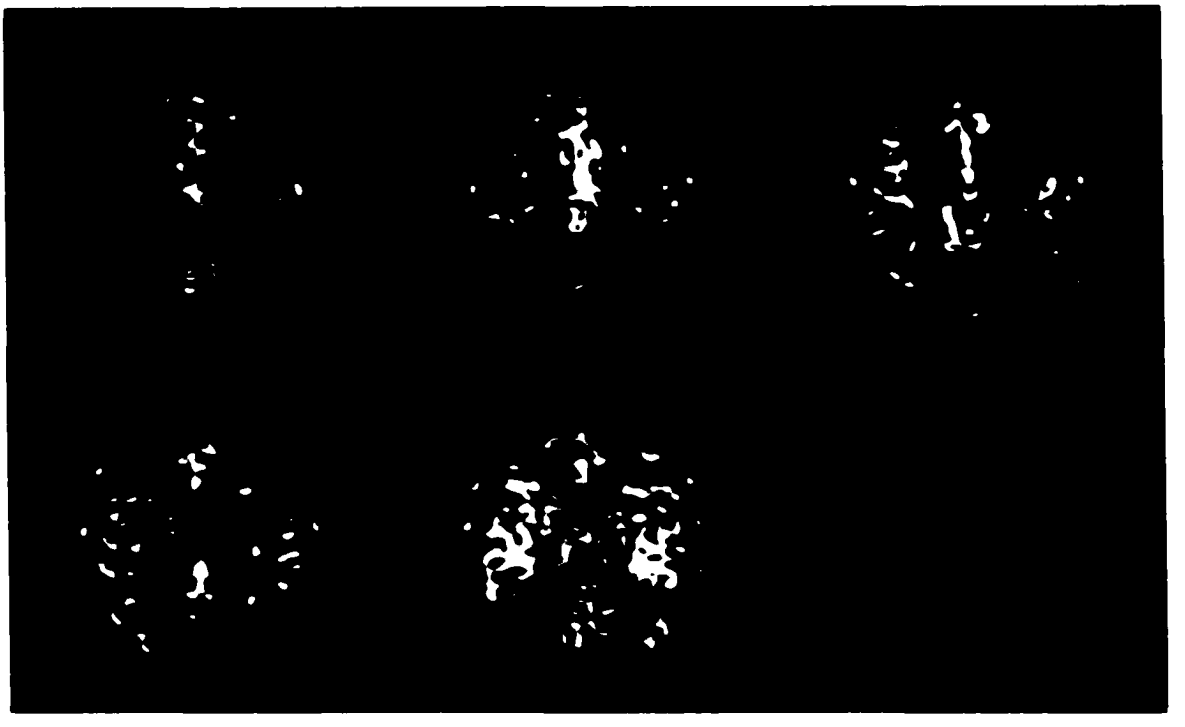


Figure 5. RI (acute stage)

Perfusion Images

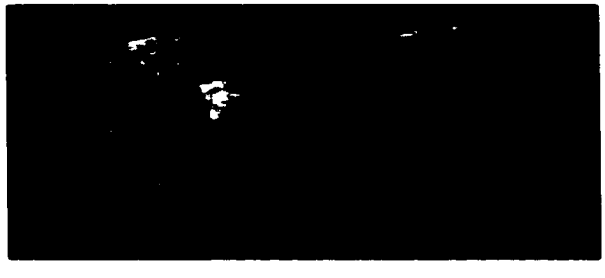


DWI

Figure 6. RI (one-month post-stroke)

Perfusion Images

DWI



T2-MRI

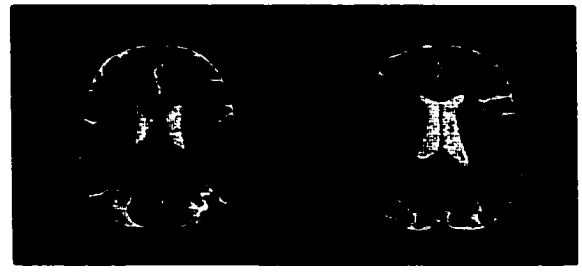


Figure 7. EJ (acute stage)

Perfusion Images

DWI

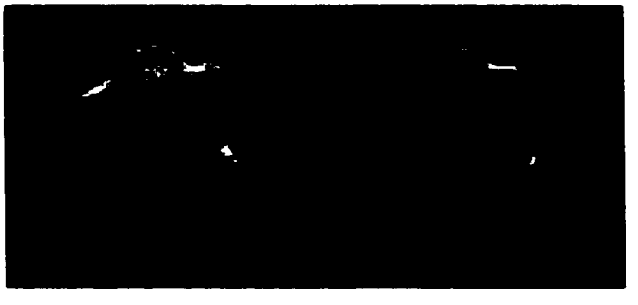


Figure 8. JT (acute stage)

Perfusion Images

DWI

Figure 9. JT (one-month post-stroke)

Perfusion Images

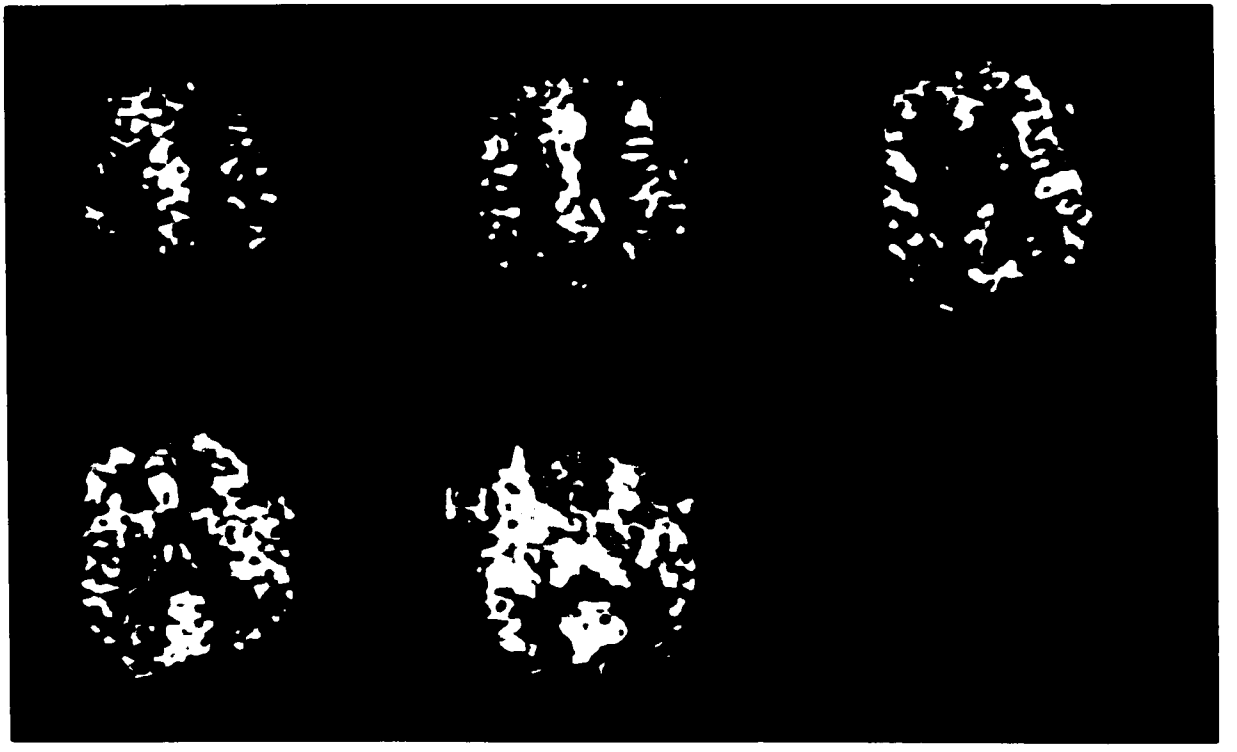
Figure 10. PH (acute stage)

Perfusion Images

DWI

Figure 11. PH (one-month post-stroke)

Perfusion Images



T2-MRI

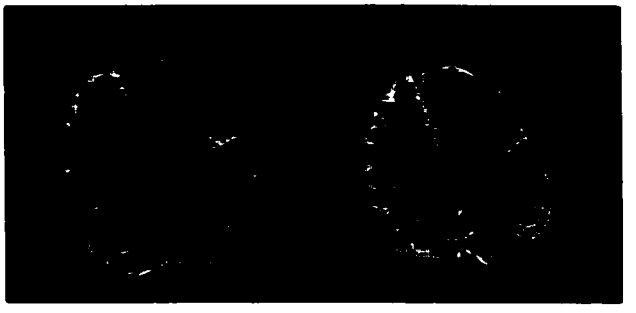


Figure 12. LN (acute stage)

Perfusion Images

DWI

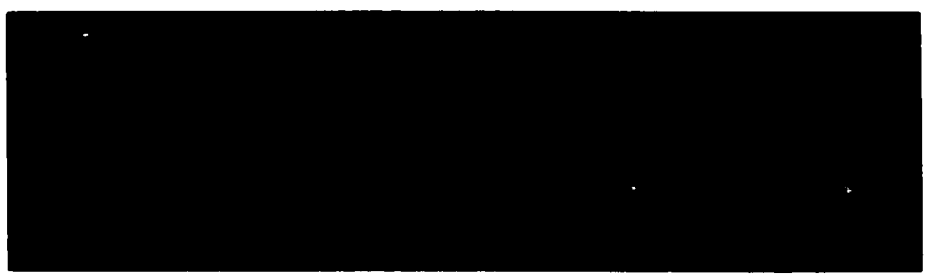
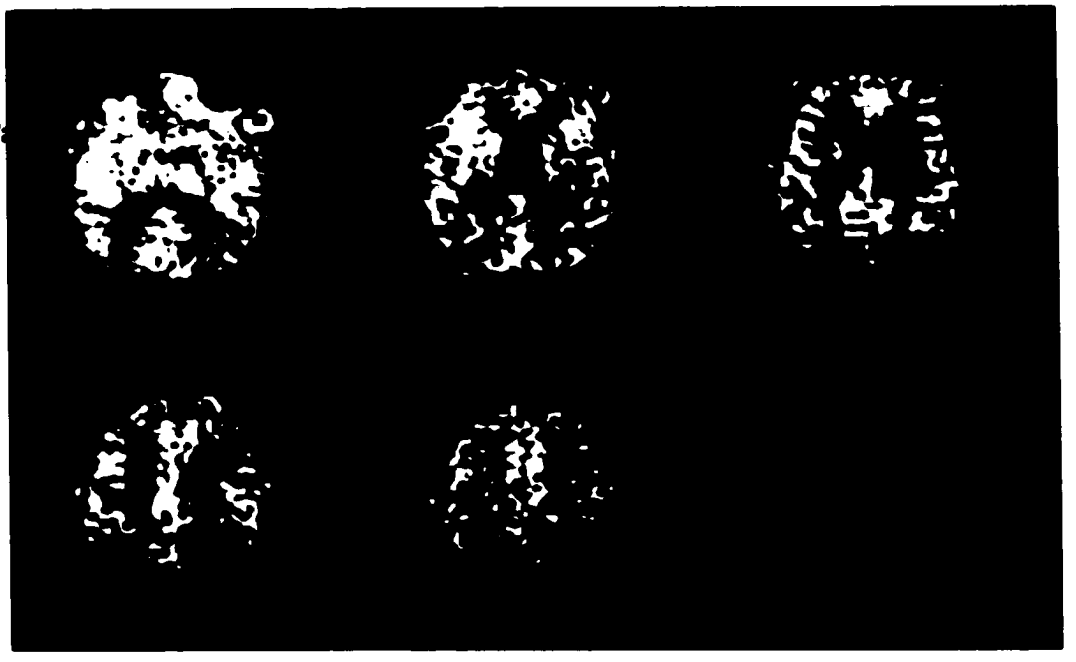


Figure 13. LN (one-month post-stroke)

Perfusion Images



T2-MRI

DWI

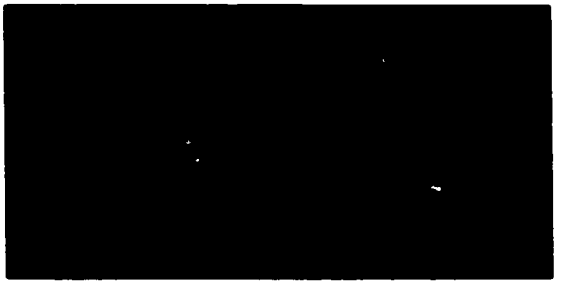


Figure 14. ES (acute stage)

Perfusion Images

DWI

Figure 15. ES (one-month post-stroke)

Perfusion Images

DWI

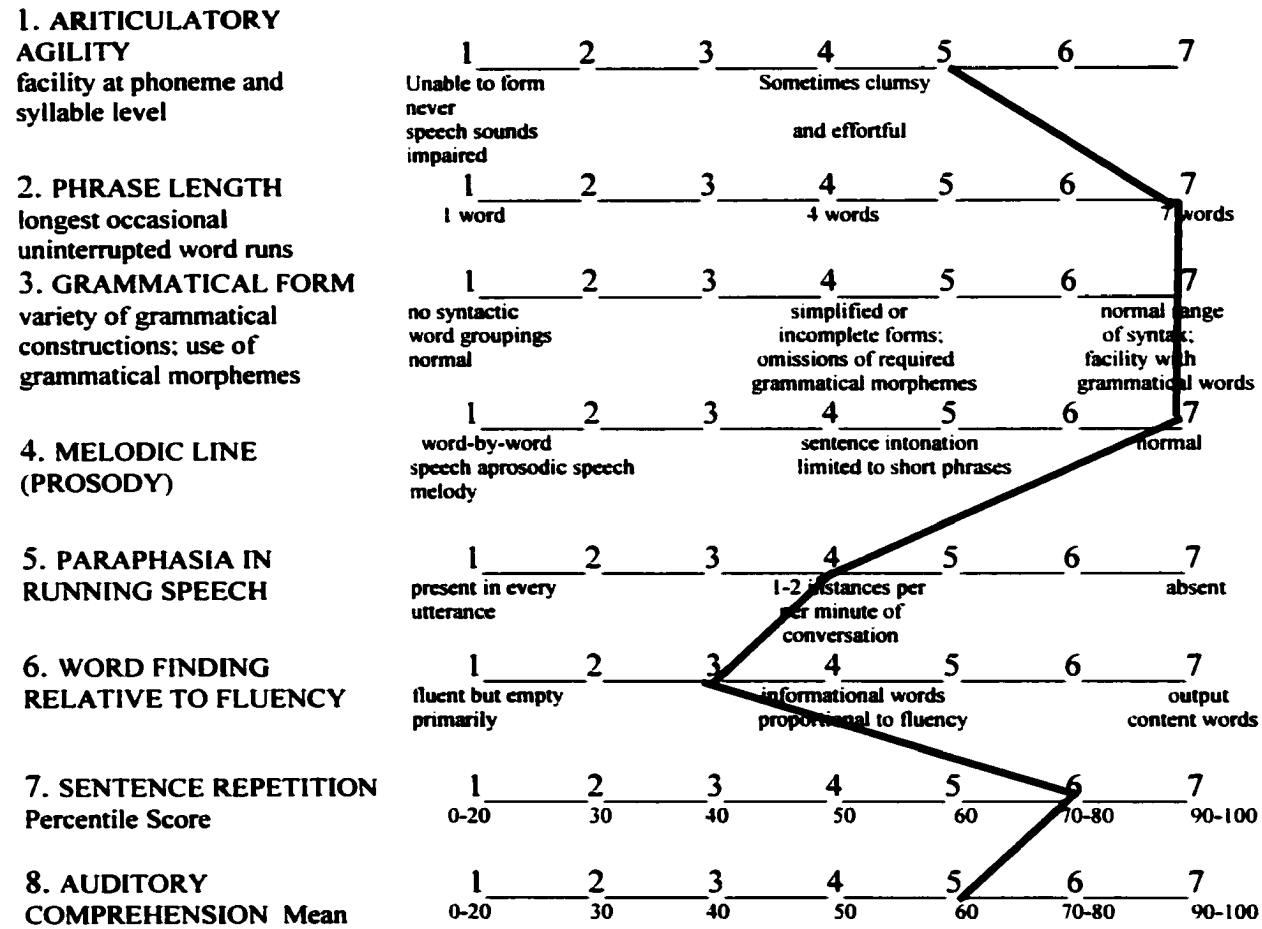
Figure 16. ES (one-month post-stroke) (Cont.)

T2-MRI

Appendix E.

LANGUAGE TEST – BDAE

Table 1. Rating Scale Profile of Speech Characteristics for CJ



VOLUME	Hypophonic	Normal	Loud
VOICE	Whisper	Normal	Hoarse
RATE	Slow	Normal	Fast

Table 2. Rating Scale Profile of Speech Characteristics for RI

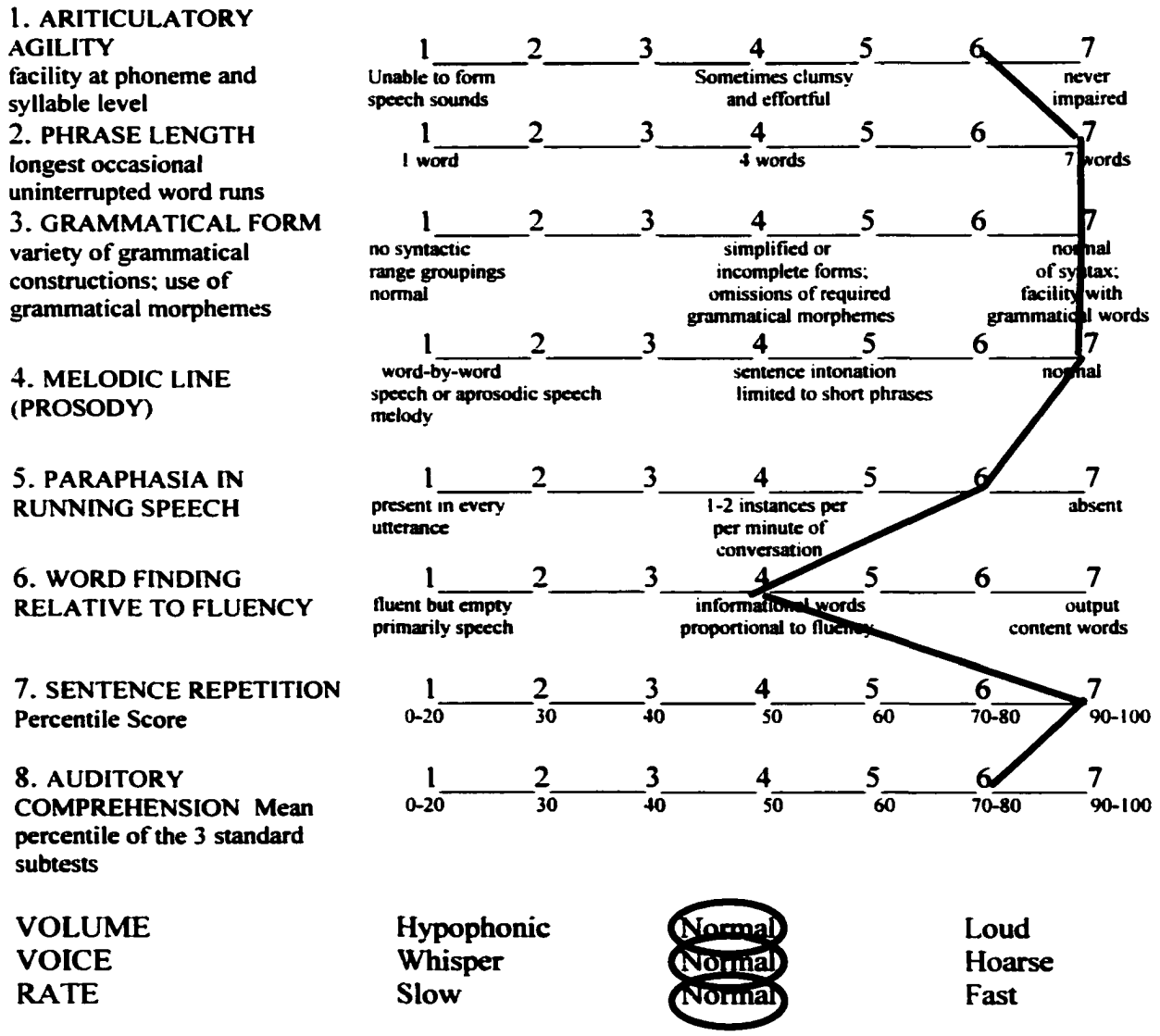
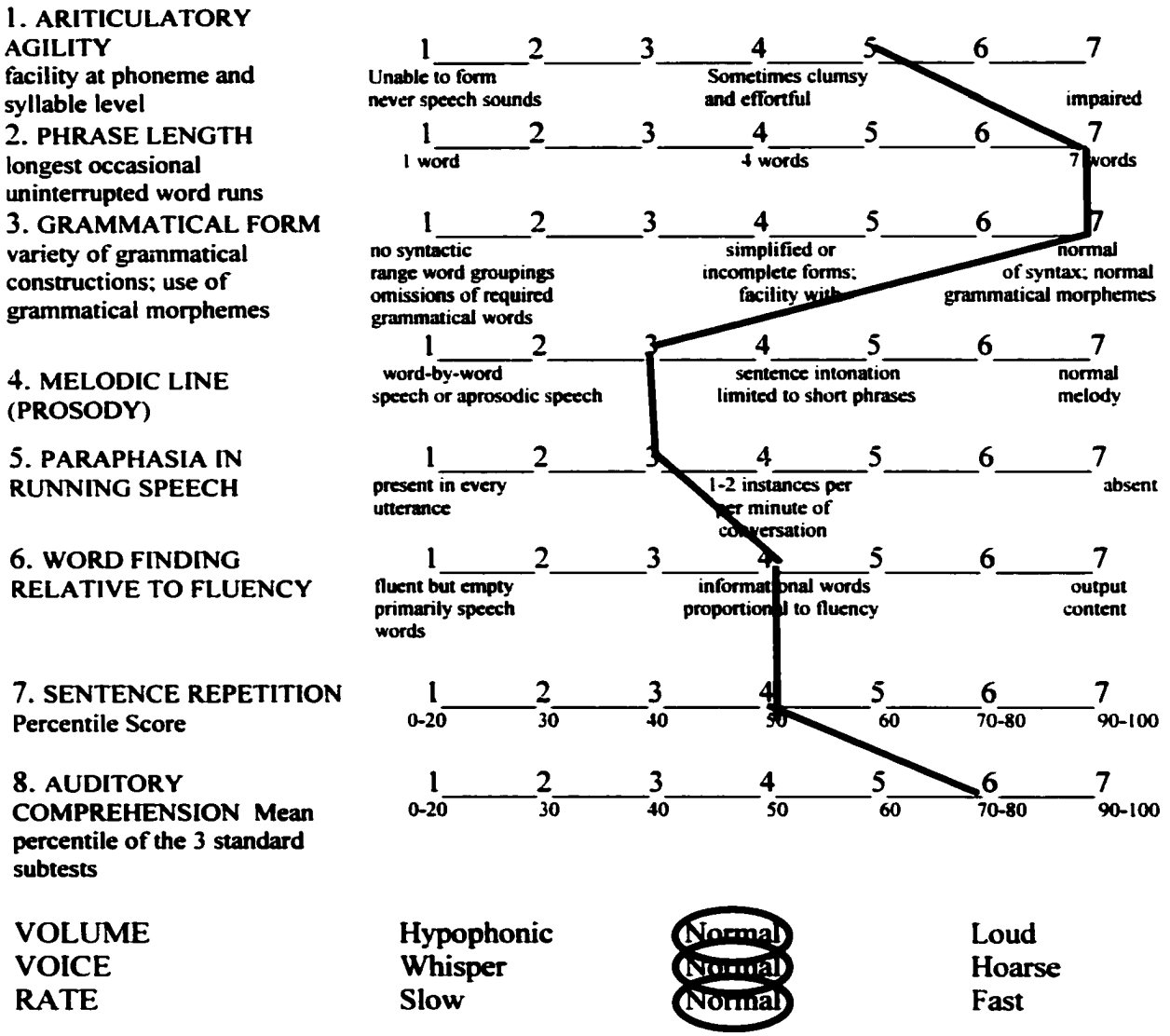
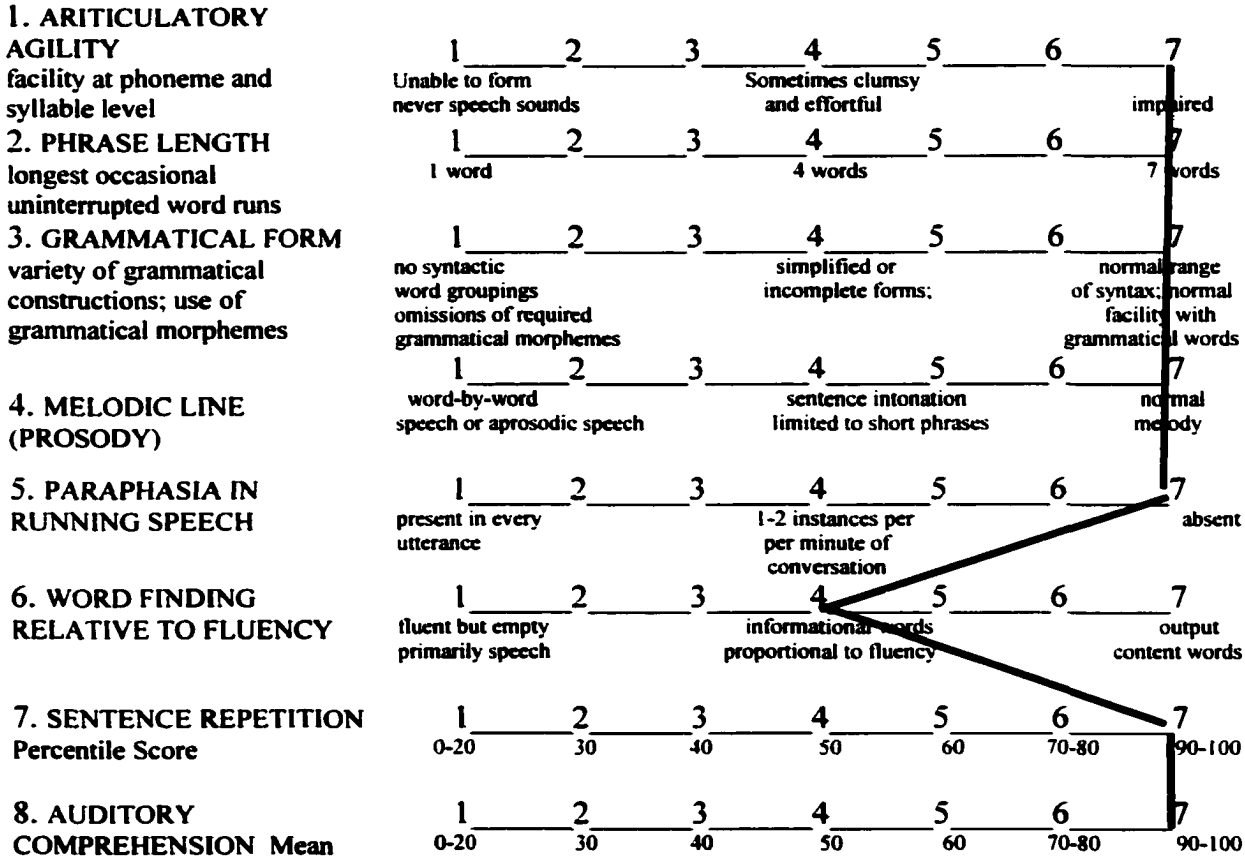


Table 3. Rating Scale Profile of Speech Characteristics for EJ



VOLUME	Hypophonic	Normal	Loud
VOICE	Whisper	Normal	Hoarse
RATE	Slow	Normal	Fast

Table 4. Rating Scale Profile of Speech Characteristics for JT



VOLUME	Hypophonic	Normal	Loud
VOICE	Whisper	Normal	Hoarse
RATE	Slow	Normal	Fast

Table 5. Rating Scale Profile of Speech Characteristics for PH

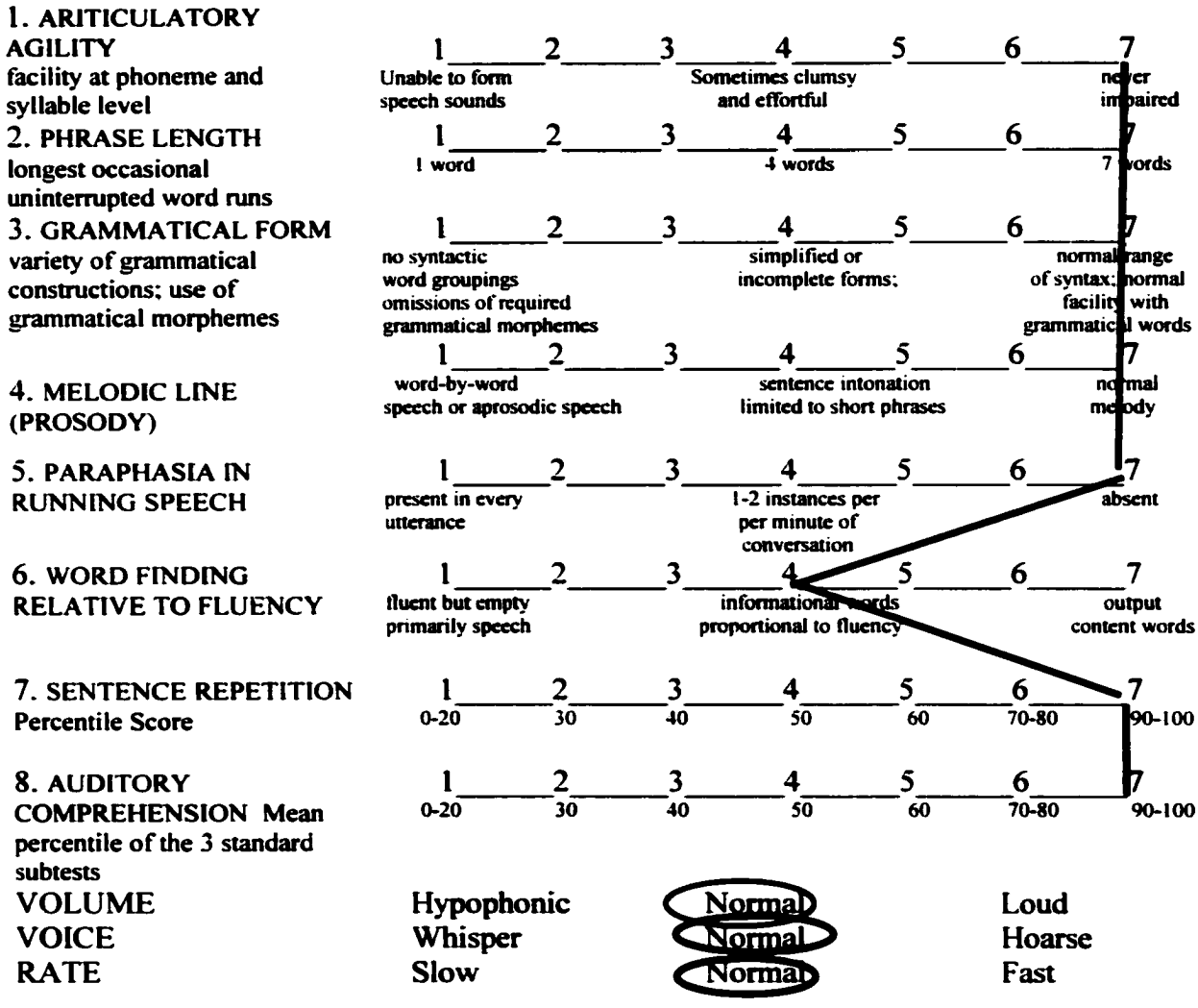
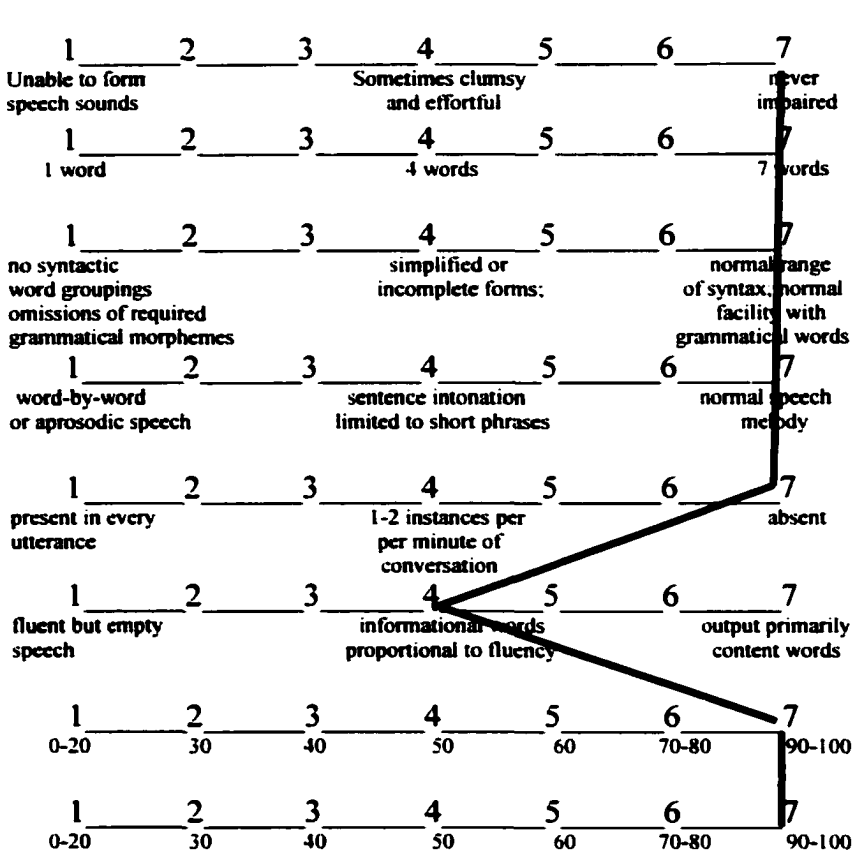
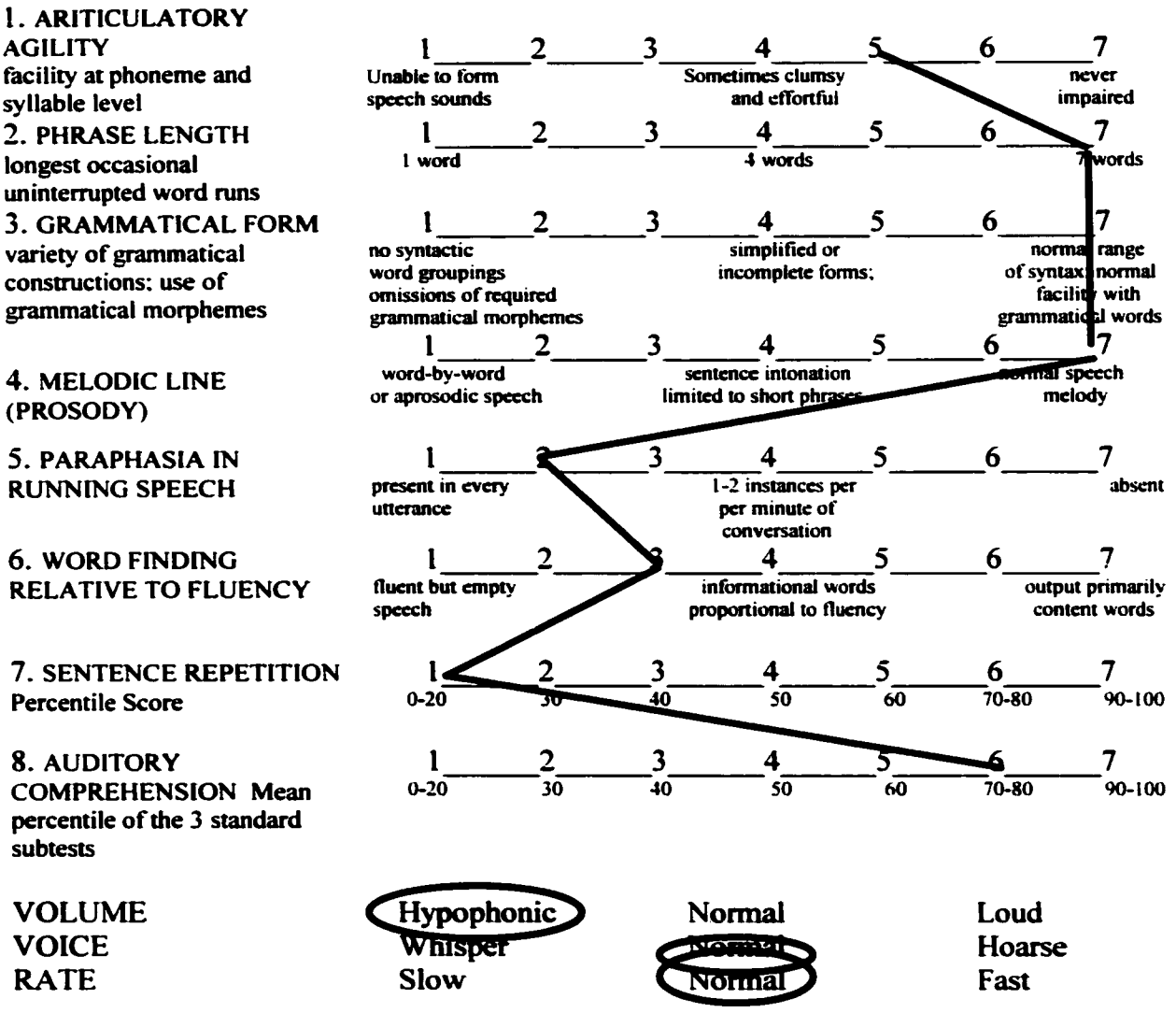


Table 6. Rating Scale Profile of Speech Characteristics for LN



VOLUME	Hypophonic	Normal	Loud
VOICE	Whisper	Normal	Hoarse
RATE	Slow	Normal	Fast

Table 7. Rating Scale Profile of Speech Characteristics for ES



References

Albers, G.W., Amarenco, P., Easton, J.D., Sacco, R.L., & Teal, P. (2001). Antithrombotic and thrombolytic therapy for Ischemic Stroke. *Chest, 119*, 300S-320S.

Ay, H., Buonanno, G.s., Rordorf, G., Schaefere, P.W., Schwamm, L.H., Wu, O., Gonzales, R.G., Yamada, K., Sorense, G.A., & Koroshetz, W.J. (1999). Normal diffusion-weighted MRI during stroke-like deficits. *Neurology, 52*, 1784-1796.

Baird, A.E. & Warach. S. (1998). Magnetic resonance imaging of acute stroke. *Journal of Cerebral Blood Flow and Metabolism, 18*, 583-609.

Barber, P.A., Darby, D.G., Desmond, P.M., Yang, Q., Gerraty, R.P., Jolley, D., Donnan, G.A., Tress, B.M., Davis, S.M. (1998). Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. *Neurology, 51*, 418-426.

Basso, A. (1992). Prognostic factors in aphasia. *Aphasiology, 6*(4), 337-348.

Basso, A., Capitani, E., & Vignolo, L.A. (1979). Influence of rehabilitation on language skills in aphasic subjects. A controlled study. *Archives of Neurology, 36*, 190-196.

Beaulieu, C., de Crespigny, A., Tong, D.C., Moseley, M.E., Albers, G.W., & Marks, M.P. (1999). Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: Evolution of volume and correlation with clinical outcome. *Annals of Neurology, 46*, 568-579.

Bowers, D., Blonder, L.X., Heilman, K.M. (1991). *The Florida Affect Battery*. Gainsville, FL: Center for Neuropsychological Studies.

Brott, T.G., Adams, H.P., Olinger, C.P., Marler, J.R., Barsan, W.G., Biller, J., Spilker, J., Holleran, R., Eberle, R., Hertzberg, V., Rorick, M., Moomaw, C.J., Walker, M. (1989). Measurements of acute cerebral infarction: a clinical examination scale. *Stroke, 20*, 864–870.

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

Cappa, S.F., Perani, D., Grassi, F., Bressi, S., Alberoni, M., Franceschi, M., Bettinardi, V., Todde, S., & Fazio, F. (1997). A PET follow-up study of recovery after stroke in acute aphasics. *Brain and Language, 56*, 55-67.

Carpenter, P.A., Just, M.A., & Reichle, E.D. (2000). Working memory and executive function: Evidence from neuroimaging. *Current Opinion in Neurobiology, 10*(2), 195-199.

Chalela, J.A., Alsop. D.C., Gonzalez-Atavales, J.B., Maldjian, J.A., Kasner, S.E., & Detre, J.A. (2000). Magnetic resonance perfusion imaging in acute ischemic stroke using continuous arterial spin labeling. *Stroke, 31*(3), 680-686.

Cherney, L.R. & Robey, R.R. (2001). Aphasia treatment: recovery, prognosis, and clinical effectiveness. In *Language Intervention Strategies in Aphasia and Related Neurogenic Communication Disorders* (4th et.) Roberta Chapey (Ed.). Philadelphia: Lippincott Williams & Wilkins.

Cote, R., Hachinski, V.C., Shurvell, B.L., Norris, J.W., & Wolfson, C. (1986). The Canadian Neurological Scale: A preliminary study in acute stroke. *Stroke, 17*, 731-737.

Ferro. J.M. (1992). The influence of infarct location on recovery from global aphasia. *Aphasiology, 6*(4), 415-430.

Finger, S., LeVere, T.E., Almli, C.R., & Stein, D.G. (1988). *Brain Injury and Recovery. Theoretical and Controversial Issues.* New York: Academic Press.

Fisher, M., Prichard, J.W., & Warach, S. (1995). New magnetic resonance techniques for acute ischemic stroke. *Journal of the American Medical Association, 274*, 901-911.

Gainotti, G. (1993). The riddle of the right hemisphere's contribution to the recovery of language. *European Journal of Communication Disorders, 28*(8), 227-246.

Gloning, K., Trappi, R., Heiss, W.D., Quatember, R. (1976). Prognosis and speech therapy in aphasia. In Lebrun, Y. & Hoops, R. (Eds.). *Recovery in Aphasia*, (pp. 57-64). Englewood Cliffs, NJ: Humanities Press.

Goldenberg, G. & Spatt, J. (1994). Influence of size and site of cerebral lesions on spontaneous recovery of aphasia and on success of language therapy. *Brain and Language, 47*, 684-698.

Goodglass, H., Kaplan, E., & Barresi, B. (2001). *Boston Diagnostic Aphasia Examination* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins.

Hacke, W., Kaste, M., Fieschi, C., Toni, D., Lesaffre, E., on Kummer, R., Boysen, G., Blumki, E., Hoexter, G., Mahagne, M.H., et al. (1995). Intravenous thromolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study. *Journal of the American Medical Association, 274*, 1017-1025.

Hacke, W., Kaste, M., Fieschi, C., von Kummer, R., Davalos, A., Meier, D., Larrue, V., Bluhmki, E., Davis, S., Donnan, G., Schneider, D., Diez-Tejedor, E., & Trouillas, P. (1998). Randomised double-blind placebo-controlled trial of thromolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). *Lancet, 352*, 1245-1251.

Heiss, W.D., Karbe, H., Weber-Luxenburger, G., Herholz, K., Kessler, J., Pietrzyk, U., & Pawlik, G. (1997). Speech-induced cerebral metabolic activation reflects recovery from aphasia. *Journal of Neurological Sciences, 145*(2), 213-217.

Helpern, J.A., Dereski, M.O., Knight, R.A., Chopp, M., & Qing, Z.X. (1993). Histopathological correlations of nuclear magnetic resonance imaging parameters in experimental cerebral ischemia. *Magnetic Resonance Imaging, 11*, 241-246.

Holland, A. L. (1989). Recovery in aphasia. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (Vol. 2, pp. 83-90). New York: Elsevier Science Publishers.

Holland, A. & Fridriksson, J. (2001). Aphasia management during the early phases of recovery following stroke. *American Journal of Speech-Language Pathology 10*, 19-29..

Holland, A.L., Greenhouse, J.B., Fromm, K., & Swindell, C.S. (1989). Predictors of language restitution following stroke: a multivariate analysis. *Journal of Speech and Hearing Research, 32*, 232-238.

Holland, A.L., Miller, J., Reinmuth, O.M., Bartlett, C., Fromm, D., Pashek, G., Stein, D., & Swindell, C. (1985). Rapid recovery from aphasia: a detailed language analysis. *Brain and Language , 24*, 156-173.

Hossman, K.A. (1997). Reperfusion of the brain after global ischemia: hemodynamic disturbances. *Shock, 8*, 95-101.

Jansen, O., Schellinger, P., Fiebach, J., Hacke, W., & Sartor, K. (1999). Early recanalisation in acute ischaemic stroke saves tissue at risk defined by MRI. *Lancet, 353*, 2036-2037.

Judd, C.M. & McClelland, G.H. (1989). *Data Analysis, A Model-Comparison Approach*. San Diego, CA: HBJ.

Kalafut, M.A. & Saver, J.L. (2000). The acute stroke subject: the first six hours. In S.N. Cohen (Ed.), *Management of Ischemic Stroke*, (pp. 17-52). New York: McGraw-Hill.

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *Boston Naming Test* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins.

Kertesz, A., Harlock, W., & Coates, R. (1979). Computer tomographic localization, lesion size and prognosis in aphasia and nonverbal impairment. *Brain and Language, 8*, 34-50.

Kertesz, A., Lau, W.K., & Polk, M. (1993). The structural determinants of recovery in Wernicke's aphasia. *Brain and Language, 44*, 153-164.

Kertesz, A. & McCabe, P. (1977). Recovery patterns and prognosis in aphasia. *Brain, 100*, 1-18.

Kidwell, C.S., Saver, J.L., Mattiello, J., Starkman, S., Vinuela, F., Duckwiler, G., Gobin, Y.P., Jahan, R., Vespa, P., Kalafut, M., & Alger, J.R. (2000). Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Annals of Neurology, 47*(4), 462-469.

Knight, R.A., Ordidge, R.J., Helpern, J.A., Chopp, M., Rodolosi, L.C., & Peck, D. (1991). Temporal evolution of ischemic damage in rat brain measured by proton nuclear magnetic resonance imaging. *Stroke, 22,* 802-808.

Lansberg, M.G., O'Brien, M.W., Tong, D.C., Moseley, M.E., & Albers, G.W. (2001). Evolution of cerebral infarct volume assessed by diffusion-weighted magnetic resonance imaging. *Archives of Neurology, 58*(4), 613-617.

Lev, M.H., Segal, A.Z., Farkas, J., Hossain, S.T., Putman, C., Hunter, G.J., Budzik, R., Harris, G.J., Buonanno, F.S., Ezzeddine, M.A., Chang, Y., Koroshtz, W.J., Gonzalez, R.G., & Schwamm, L.H. (2001). Utility of perfusion-weighted CT imaging in acute middle cerebral artery stroke treated with intra-arterial thrombolysis. *Stroke, 32,* 2021-2034.

Li, F., Silva, M.D., Sotak, C.H., & Fisher, M. (2000). Temporal evolution of ischemic injury evaluated with diffusion-, perfusion-, and T2-weighted MRI. *Neurology, 54*(3), 689-697.

Lopez, O.L., Becker, J.T., Klunk, W., Saxton, J., Hamilton, R.L., Kaufer, D.I., Sweet, R.A., Cidis Meltzer, C., Wisniewski, S., Kamboh, M.I., & Dekosky, S.T. (In press, a). Research evaluation and diagnosis of probable Alzheimer's disease oer the last two decades, I. *Neurology.*

Lopez, O.L., Becker, J.T., Klunk, W., Saxton, J., Hamilton, R.L., Kaufer, D.I., Sweet, R.A., Cidis Meltzer, C., Wisniewski, S., Kamboh, M.I., & Dekosky, S.T. (In press, b). Research evaluation and diagnosis of probable Alzheimer's disease oer the last two decades, II. *Neurology.*

Loesche, J. & Steward, O. (1977). Behavioral correlates of denervation and reinnervation of the hippocampal formation of the rat: recovery of alternation performances following unilateral entorhinal cortex lesions. *Brain Research Bulletin, 2*, 31-39.

Lovblad, K., Baird, A.E., Schlaug, G., Benfield, A., Siewert, B., Voetsch, B., Conor, A., Burzynski, C., Edelman, R., & Warach, S. (1997). Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. *Annals of Neurology*, 42(2), 164-169.

Mahoney, F.L. & Barhel, D.W. (1965). Functional evaluation: the Barthel Index. *Maryland State Medical Journal, 14*, 2.

Marks, M.P., Tong, D.C., Beaulieu, C., Albers, G.W., de Crespigny, A., & Moseley, M.E. (1999). Evaluation of early reperfusion and IV tPA therapy using diffusion- and perfusion-weighted MRI. *Neurology, 52*, 1798-1792.

Marshall, R.C., Tompkins, C.A., & Phillips, D.S. (1982). Improvement in treated aphasia: examination of selected prognostic factors. *Folia Phoniatrica, 34*, 304-315.

Mazzoni, M., Vista, M., Pardossi, L., Avial, L., Bianchi, F., & Moretti, P. (1992). Spontaneous evolution of aphasia after ischaemic stroke. *Aphasiaology, 6*, 387-369.

Meldrum, B. (1985). Possible therapeutic applications of antagonists of excitatory amino acid neurotransmitters. *Clinical Science, 68*, 113-122.

Messerli, P., Tissot, A., & Rodriguez, J. (1976). Recovery from aphasia: some factors of prognosis. In Y. Lebrun and R. Hoops (Eds.), *Recovery in Aphasia*, (pp. 124-135). Englewood Cliffs, NJ: Humanities Press.

Metter, E.J., Hanson, W.R., Jackson, C.A., Kempler, D., van Lancker, D., Maziotta, J.C., & Phelps, M.E. (1990). Temporoparietal cortex in aphasia evidence from positron emission tomography. *Archives of Neurology, 47*, 1235-1238.

Metter, E.J., Jackson, C.A., Kempler, D., & Hanson, W.R. (1992). Temporoparietal cortex and the recovery of language comprehension in aphasia. *Aphasiology, 6*(4), 349-358.

Moseley, M.E., Cohen, Y., Kucharczyk, J., Mintorovich, J., Asgari, H.S., Wendland, M.F., Tsuruda, J., & Norman, D. (1990). Diffusion-weighted MR imaging of anisotropic water diffusion in cat cetral nervous system. *Radiology, 176*, 439-445.

Naeser, M.A., Gaddie, A., Plumbo, C.L., & Stiassny-Eder, D. (1990). Later recovery of auditory comprehension in global aphasia. *Archives of Neurology, 47*, 425-432.

Neumann-Haefelin, T., Moseley, M.E., & Albers, G.W. (2000). New magnetic resonance imaging methods for cerebrovascular disease: emerging clinical applications. *Annals of Neurology, 47*(5), 559-570.

Nieto-Sampedro, M., Manthrope, M., Barbin, G., Varon, S., & Cotman, C.W. (1983). Injury-induced neuronotrophic activity in adult rat brain: correlation with survival of delayed implants in the wound cavity. *Journal of Neuroscience, 3*, 2219-2229.

Olin, J.J. (2001). Cognitive function after systemic therapy for breast cancer. *Oncology, 15*(5), 613-618.

Overgaard, K., Sereghy, T., Boysen, G., Pedersen, H., Diemer, N.H. (1992). Reduction of infarct volume and mortality by thrombolysis in a rat embolic stroke model. *Stroke, 23*(8), 1167-1173.

Pashek G.V. & Holland, A.L. (1988). Evolution of aphasia in the first year post-onset. *Cortex, 24*, 411-423.

Pedersen, P.M., Jorgensen, H.S., Nakayama, H., Raaschou, H.O., & Olsen, T.S. (1995). Aphasia in acute stroke: incidence, determinants, and recovery. *Annals of Neurology, 38*(4), 659-666.

Raisman, G. (1969). Neuronal plasticity in the septal nuclei of the adult rat. *Brain Research, 14*, 25-48.

Rothman, S.M. (1983). Synaptic activity mediates death of hypoxic neurons. *Science, 220*, 536-537.

Rubens, A.B. (1977). The role of changes within the central nervoues system during recovery from aphasia. In M. Sullivan & M.S. Kommers (Eds.), *Clinical aphasiology conference proceedings*, (pp. 1-4). Minneapolis: BRK.

Sarno, M.T., & Levita, E. (1971). Natural course of recovery in severe aphasia. *Archives of Physical Medicine and Rehabilitation, 52*, 175-178.

Schallert, T., Kozlowski, D.A., Humm, J.L., & Cocke, R.R. (1997). Use-dependent structural events in recovery of function. *Brain Plasticity, Advances in Neurology, 73*, 229-238.

Scheinberg. P. (1991). The biologic basis for the treatment of acute stroke. *Neurology, 41*, 1867-1873.

Schellinger, P.D., & Jansen, O., Fieback, J.B., Heiland, S., Steiner, T., Schwab, S., Pohlers, O., Ryssel, H., Sartor, K., & Hacke, W. (2000). Monitoring intravenous recombinant tissue plasminogen activator thrombolysis for acute ischemic stroke with diffusion and perfusion MRI. *Stroke, 38*,1318-1328.

Schlaug, G., Benfield, B.S., Baird, A.E., Stewert, B., Lovblad, K.O., Parker, R.A., Edelman, R.F., Warach, S. (1999). The ischmic penumbra. Operationally defined by diffusion and perfusion MRI. *Neurology, 53*(7), 1528-1538.

Schuell, H. (1954). Clinical observations on aphasia. *Neurology, 4*, 179-189.

Schwamm, L.H., Koroshetz, W.J., Sorensen, A.G., Wang, B., Copen, W.A., Budzik, R., Rordorf, G., Buonanno, F.S., Schaefer, P.W., & Gonzalez, G. (1998). Time course of lesion development in patients with acute stroke. Serial diffusion- and hemodynamic- weighted resonance imaging. *Stroke, 29*, 2268-2276.

Shisler, R.J., Baylis, G.C., & Frank, E.M. (2000). Pharmacological approaches to the treatment and prevention of aphasia. *Aphasiology, 14*(12), 116-1186.

Simon, R.P., Swan, J.H., Griffiths, T., & Meldrum, B.S. (1984). Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science, 226*, 850-852.

Stein, D.G. & Glasier, M.M. (1992). An overview of developments in research in recovery from brain injury. In F.D. Rose & D.A. Johnson (Eds.), *Recovery From Brain Damage. Reflections and Directions*. New York: Plenum Press.

Stroke incidence presented by the *American Stroke Association* (2000). Retrieved September 5, 2000, from http://www.strokeassociation.org/

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995). Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine, 333*, 1581-1587.

Thulborn, K.R., Carpenter, P.A., & Just, M.A. (1999). Plasticity of language-related brain function during recovery from stroke. *Stroke, 30*, 749-754.

Tong, D.C., Yenari, M.A., Albers, G.W., O'Brien, M., Marks, M.P., & Moseley, M.E. (1998). Correlation of perfusion- and diffusion- weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke. *Neurology, 50*, 864-869.

Weisenburg, T. & McBride, K. (1935). *Aphasia*. New York: The Commonwealth Fund.

West, J.F., Sands, E.S., & Ross-Swain, D. (1998). *Bedside Evaluation Screening Test*, 2nd ed. Austin, TX: Pro-Ed.

Zivin, J.A., Fisher, M., DeGirolami, U, Hemenway, C.C., & Stashak, J.A. (1985). Tissue plasminogen activator reduces neurological damage after cerebral embolism. *Science. 230(4731),* 1289-1292.

Zivin, J.A., Lyden, P.D., DeGirolami, U., Kochhar, A., Mazzarella, V., Hemenway, C.C., & Johnston, P. (1988). Tissue plasminogen activator. Reduction of neurologic damage after experimental embolic stroke. *Archives of Neurology, 45*(4), 387-391.