THE SPEECH-RELATED NEURAL ACTIVITY OF INDIVIDUAL STUTTERERS AND GROUPS OF STUTTERERS: A COMPARISON

by

SARAH ELISABETH THOM

(Under the Direction of Dr. Anne Bothe)

ABSTRACT

Purpose: To (a) investigate neural activity of individuals who stutter, and (b) compare individual results with previously published data from groups of stutterers.

Method: Three adult stutterers completed 5 PET imaging sessions consisting of 6 scans, two for each of three conditions: eyes closed rest, oral paragraph reading, and monologue. Data from these scans were qualitatively assessed to determine neural activity patterns and compared to previously published group data.

Results: Individual data analysis showed significant discrepancies in neural activity among participants. No distinct activity pattern emerged and no specific hemisphere or neural region appeared noteworthy. Compared to group data, the lack of remarkable activity contradicts previously published group data.

Conclusions: Discrepancies between individual and group data raise concerns regarding the implications of group studies of stutterers. Future research should examine group and individual data to determine the fundamental nature of stuttering and function as an aid to developing clinical implications.

INDEX WORDS: Stuttering; PET; brain imaging; inter-subject averaging

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DEDICATION

"Whatever you do, work heartily, as for the Lord and not for men, knowing that from the Lord you will receive the inheritance as your reward. You are serving the Lord Christ."

Colossians 3:23-24

"I can do all things through Him who strengthens me."

Philippians 4: 13

To my parents, whose lives have been evidence of the power of persistence and hard-work. To my family and friends, whose prayers and words of encouragement have been an ever-present reminder that I have not made this journey alone. To my editor, my coach, my confidant, my best friend, my husband; you have been a crucial part of this accomplishment. Thank you for encouraging me to take a chance, believing in me when I could not believe in myself, and pushing me to work hard and accomplish great things. And finally to my God, without whom I can do nothing. May Your name be glorified by the work embodied here.

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Outside of academia, the members of my church small group played a part in this accomplishment by providing steady encouragement over the past 2 years. From cooking dinners to covering me with prayer, these friends reminded me that this task was God's perfect plan for me. Lastly, my sweet husband has served many roles in helping me with this task: advisor, sounding board, cheerleader, to name a few. He has put up with 2 long years of studying, writing, researching, editing, et cetera. I could not have completed a project like this without his patient love and support.

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CHAPTER 1: REVIEW OF LITERATURE

As we begin the 21st century, the predominant hypothesis regarding stuttering theory and research is that developmental stuttering is caused by central nervous system (CNS) dysfunction with probable genetic roots (Ingham, Fox, Ingham, Zamarripa, Martin, Jerabek et al., 1996). This centrality of neurophysiology to stuttering research is the result of almost a century of research in a variety of areas, with an extensive array of successes, debates, and dilemmas. The purpose of this section is to give an account of the history, emergence, and significance of neurophysiology in stuttering research.

Role and Influence of Cerebral Dominance Theories

In his review of research regarding the "organicity," or organic etiology of stuttering, Van Riper (1982) discussed some of the earliest notions regarding brain function and stuttering. Some beliefs about the cause of stuttering in the 19th and early 20th centuries included that it was a deficit in cortical inhibition, a malfunctioning medulla oblongata, a deficient cerebral cortex, a lesioned cuneus (at the base of the occipital lobe) impairing visual imagery, or a type of aphasia (Van Riper, 1982).

Perhaps most noteworthy among the first neurological descriptions of stuttering was a theory proposed by S.T. Orton and L.E. Travis (Bloodstein, 1995; Van Riper, 1982) called the Cerebral Dominance Theory (CDT) (Travis, 1978). Orton and Travis, among the first to investigate CNS dysfunction as a possible explanation for stuttering, focused their research on the hemispheric interactions of the brain and introduced the overall idea that stutterers possess different neurophysiology than nonstutterers. This

concept was born from observations which suggested that the bilaterally paired musculature used during speech worked independently in stutterers. Orton and Travis hypothesized this difference was the result of incomplete or inappropriate language lateralization in stutterers, and thus maintained that stuttering resulted from an abnormal neurologic system (Bloodstein, 1995; Orton, 1928; Travis, 1931).

This idea, referred to as the Orton-Travis theory (Bloodstein, 1995; Packman & Attanasio, 2004) or Cerebral Dominance Theory (CDT), found considerable support during the 1920s, 1930s, and 1940s, and a variety of physiological studies were performed which provided corroborating evidence (Moore, 1993). Travis' electromyography (EMG) study in 1934 tested his own hypothesis, in which he recorded the electrical potentials from the left and right masseter muscles of both stutterers and nonstutterers and found no differences between the two groups' muscle movements during typical speech, though during stuttered moments differences were clearly evident.

This apparent support of the CDT was questionable, however; it relied upon behavior observed solely during the act of stuttering, and thus raised the question of whether the muscle movement discrepancies were a cause or an effect of stuttering (Bloodstein, 1995). Williams (1955) replicated Travis' study with a few methodological changes and found many similar results. He also found that the discrepant muscle movements could be found in nonstutterers when they performed "fake" stuttering. Interestingly, he also discovered that the discrepant movements in both groups were alike when they were instructed to silently move their jaws in certain patterns. This discovery marked the beginning of a shift in the popularity of hemispheric dominance research. Beginning in the late 1940s and throughout the 1950s, not only did research regarding

cerebral dominance decline, but theories similar to the CDT to explain stuttering were less accepted (Moore, 1993). Moore (1993) explains this decline, pointing to problematic research and stating that

> "…the technology was new, there was no resorting to authority for research design, we were a new profession with little research data or laurels, physiological research was difficult stuff at best, and the utility of this line of research was difficult to see given the prevalent theories of the 1950s and 1960s." (p. 40)

Overall, the significance of the CDT began to appear questionable, and research regarding cerebral dominance seemed inconsequential.

In the mid-1960s, however, hemispheric processing research was revived. R. K. Jones performed a study in 1966 using the Wada intracarotid amytal test (Wada, 1949; Wada & Rasmussen, 1960) on four stutterers. This test requires an injection of an anesthetic, typically sodium amytal, via one internal carotid artery. The injection was performed one hemisphere at a time and was essentially designed to disable the language and memory functions of one hemisphere in order to evaluate the operation of the other (Bloodstein, 1995). While more current research has shown that this test is not a valid measure of language dominance (Benbadis, Binder, Swanson, Fischer, Hammeke, Morris et al., 1998), at the time that Jones used this technique is was considered quite reliable. Surprisingly, during the test Jones observed that his participants demonstrated transient aphasia when the drug was given to *either* the right or the left artery, indicating bilateral cortical control of speech (Van Riper, 1982). This evidence suggested that Travis' (1931) idea regarding hemispheric differences in stutterers was indeed correct.

Curry and Gregory solidified the resurgence of the CDT in 1969 when they used dichotic listening procedures to evaluate language lateralization (Moore, 1993). Dichotic listening requires the listener to attend to two different auditory signals concurrently, one of which is presented in the left ear and one in the right (Bloodstein, 1995; Van Riper, 1982). Initial studies using this procedure demonstrated consistent differences in the left and right ears in the type and number of acoustic signals correctly identified by listeners (Moore, 1993). Listeners' right ears scored higher on verbal material, being contralateral to the language dominant left hemisphere, and listeners' left ears performed more accurately for nonverbal material, being contralateral the right hemisphere, presumed to be more dominant for this type of stimuli.

Two significant findings resulted from Curry and Gregory's (1969) study. First, 45% of the stutterers showed the expected right-ear advantage on the dichotic word test, compared to 75% of their controls. Secondly, the difference between left and right ear scores for the nonstutterers was an average of more than twice the scores of the stutterers (Bloodstein, 1995). So in sum, Curry and Gregory's (1969) data suggested that (a) stutterers have a smaller right-ear advantage than nonstutterers and (b) do not show the large discrepancies between performance of the left and right ears seen in nonstutterers during dichotic listening tasks. These data seemed to add support for the CDT of stuttering and also provided a less invasive method than the Wada test to assess the laterality of language (Bloodstein, 1995; Moore, 1993).

With research regarding hemispheric processing once again renewed, studies similar to Curry and Gregory's (1969) dichotic listening tests became plentiful (Moore, 1993). While much of the data from these studies continued to demonstrate dichotomous

ear performances between stutterers and nonstutterers, some studies failed to find a right ear advantage in all stutterers (Bloodstein, 1995; Moore, 1993; Van Riper, 1982). These discrepant results from the dichotic listening studies proved disconcerting in the push to substantiate hemispheric theory and research (Van Riper, 1982).

Other areas of study in the search to understand the cerebral dominance of stuttering included investigations of tachistoscopic viewing and auditory tracking, although results from these studies were too inconsistent to support any significant conclusions (Bloodstein, 1995; Moore, 1993; Van Riper, 1982). Several researchers began to investigate handedness as well. A common belief in the early 20th century was that shifting an individual's handedness would create emotional upheaval that would result in stuttering. While some studies showed stuttering after shifting individuals' handedness, others did not; in short, this theory was never fully corroborated (see Van Riper, 1982, p. 337, for list of studies). In fact, Van Riper asserted that the more pressing research question was whether stutterers differ from nonstutterers in *central* rather than *peripheral* laterality, leading him to conclude that the "hounds of research were barking up the wrong tree" (Van Riper, 1982, p. 338).

Theories of Speech Motor Control and Stuttering

While the emphasis on cerebral dominance investigations waxed and waned, another perspective emerged that became one of the most popular arguments in favor of a neurophysiologic perspective regarding stuttering. From this perspective, known as the Speech Motor Control (SMC) viewpoint, stuttering was considered a disorder resulting

from an atypical speech motor system (Ingham, 1998)[1]. The SMC perspective, with roots extending as far back as Travis' (1934) EMG study of the facial muscles of stutterers, or perhaps to Wingate's Modified Vocalization Hypothesis (1969, 1970), was made popular by the Articulatory Dynamics (AD) model (Zimmermann, 1980c). This model espoused three fundamental beliefs about stutterers: that they display (a) asynchronous movements during articulation of stutter-free speech, (b) atypical timing and variability in their stutter-free speech, and (c) muscle oscillations similar to tremors concurrent with stuttering (Zimmermann, 1980a, 1980b).

Zimmerman's investigations, however, were shown to have potentially fatal flaws, as highlighted by Goldsmith's (1983) letter to the editor in reference to Zimmermann's initial study. Goldsmith pointed out, for example, that Zimmerman's studies failed to control for confounding factors, such as participant age and gender, which could have accounted for the unique characteristics among the stuttering participants. Subsequent studies also emerged that did not corroborate Zimmerman's evidence of the three fundamental beliefs of the AD model. By the mid-1990s, the cumulative evidence demonstrated that the model offered minimal proof of its claims. In fact, while studies within the SMC framework have continued, very little noteworthy evidence has been provided by SMC-based research. In fact, much of the research (see Ingham, 1998, p. 71) showing discrepancies between stutterers and normally fluent speakers and aiming to support the legitimacy of the SMC perspective has merely demonstrated differences in speech production patterns rather than a damaged central system. Ingham and Cordes (1997) argued that these differences have never been shown

[1] The following description and discussion of the SMC perspective and its contribution to stuttering theory and treatment is based largely upon the comprehensive review of this area of research by Ingham (1998; pp. 69-76).

to be opposed to normal speech, as the proponents of the SMC viewpoint liked to suggest. In the grand scheme of scholarly and therapeutic value, this line of research proved to offer very little of consequence in terms of improved understanding of stuttering and how to effectively treat it.

Overall, while cerebral dominance and speech motor control theories during the 19th and 20th centuries produced a plethora of information about stuttering and helped to define the disorder, they failed to offer irrefutable evidence that the etiology of stuttering was organic or neurological (Ingham, 1998; Van Riper, 1982). Indeed, as Bloodstein (1995) so aptly pointed out, the evidence leading up to the 21st century pointing to a true discrepancy between stutterers and nonstutterers in cerebral dominance regarding language lateralization was, while remarkable, too inconsistent and ultimately inconclusive. Similarly, the impetus to investigate stuttering from an SMC perspective faded as contradictory results became commonplace in this area of research. It was during this very time, however, that researchers began to utilize neuroimaging to investigate the disorder and a neuroscience orientation to stuttering research began to emerge (Ingham, 1998).

Neuroimaging and Stuttering

Numerous brain imaging techniques are currently used in stuttering research and are based on two distinct modalities, *electric-magnetic* and *hemodynamic-metabolic* (Horwitz, Friston, & Taylor, 2000). Electroencephalography (EEG), the less expensive and more common of the two electric-magnetic techniques, is a measurement of electrical activity in the brain. EEG provides a simultaneous measure of both the timing and

sequencing of neural events, in contrast to hemodynamic-metabolic methods, which can take nearly 40 seconds to acquire the necessary data for constructing an image of blood flow in the brain (Posner & Raichle, 1994).

Two studies performed in the early 1980s used EEG to investigate alpha-wave activity in stutterers (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; Moore, 1984). In the first study, 11 stutterers showed disproportionate right hemisphere alpha-wave activity that shifted to the left hemisphere after treatment (Boberg et al., 1983). Moore (1984) replicated this finding in a single-subject design. These results suggested that the *degree* of hemispheric lateralization may play a part in the functional control of stuttering (Ingham, 2001). A few decades later, event-related potentials (ERP) were measured; results indicated that stutterers displayed atypical auditory processing in the right hemisphere, specifically suppression of early auditory processing in the right auditory cortex for spoken and listened speech sounds that was not demonstrated in the nonstuttering controls (Liotti, Ingham, Ingham, Kothmann, Perez, & Fox, 2001). It is important to note that a significant limitation of EEG technology is its susceptibility to movement artifacts (i.e., additional data points caused by mere movement). Thus, it is difficult to determine whether any experimental effect should be attributed to speech processing, the movement inherent in speech, or the additional movement that often occurs in stuttering.

While EEG is used to measure the electrical currents associated with neural activity, another electric-magnetic method, MEG, is used to record the magnetic fields that are created by those electrical currents (Horwitz et al., 2000). This method is also useful for its high temporal resolution, though a salient limitation is that is not suited for

investigating subcortical regions of the brain (Ingham, 2003). Despite this limitation, MEG methodology has still been utilized in stuttering research. Salmelin and colleagues have shown that stutterers display atypical activations in the right auditory cortex during stimulation (Salmelin, Schnitzler, Schmitz, Jäncke, Witte, & Freund, 1998) as well as a unique order of activation in neural regions associated with typical speech (Salmelin, Schnitzler, Schmitz, & Freund, 2000). For example, when Salmelin and colleagues employed stutterers in a single word reading task, they first observed activations in the left motor cortex, known for motor planning, followed by left inferior frontal activations, regions used in articulatory programming, which nonstutterers showed the opposite order of activations. Atypical activations in the left inferior frontal and right rolandic areas have also been shown (Biermann-Ruben, Salmelin, & Schnitzler, 2005). Additionally, inadequate preparatory brain activity for speech, or an impaired ability to anticipate speaking, has been demonstrated (Walla, Mayer, Deecke, & Thurner, 2004). Replication of these results, however, is still needed.

In addition to these imaging approaches, various hemodynamic, or cerebral blood flow (CBF) techniques, exist to investigate the neural regions associated with behavior (Posner & Raichle, 1994). These methods are based upon a hypothesis that changing neural activity will incur changes in CBF (Horwitz et al., 2000). This idea was borne out of research by Charles Sherrington (1906), whose initial work demonstrated that an increase in CBF is associated with increases in neuronal firing. A unique single-subject study by Fulton (1928) not only confirmed this discovery but was also the first to demonstrate a CBF task-habituating effect (i.e., a gradual decrease in the extent of CBF activation that occurs when a task becomes more familiar) (Ingham, 2001).

Single photon emission tomography (SPECT) is a CBF measurement procedure used to assess single plane brain slices (Ingham, 1998). Pool and colleagues used SPECT and found discrepancies between stutterers and nonstutterers in at-rest patterns of hemispheric asymmetries; specifically, stutterers displayed increased activity in right hemisphere regions associated with speech motor control (e.g., anterior cingulate, superior temporal, and middle temporal gyri). This study, considered the first *functional-lesion investigation* (i.e., a study which attempts to identify regional physiological abnormalities stemming from a disorder rather than gross physical anomalies), suggested a possible "stutterer-specific trait" (Ingham, 2001). This is a disputed finding, however, as several subsequent studies failed to replicate some of Poole et al.'s assertions (Ingham, 1998; Ingham, Fox, & Ingham, 1996).

fMRI is another method of tracking CBF by recording blood oxygenation and volume levels that result from changing neural activity, a technique known as blood oxygenation level-dependent contrast (BOLD) (Horwitz et al., 2000; Ingham, 1998). An advantage of fMRI is that it produces high temporal resolution, and is thus useful in accurately pinpointing the timing of neural activity. Several fMRI studies have been performed in stuttering research. One simply showed that this technique can be successfully used in studies requiring overt speech (Preibisch, Raab, Neumann, Euler, von Gudenberg, Gall et al., 2003). Van Borsel and colleagues showed that stutterers lacked bilateral auditory activations during speech as well as demonstrated increased right hemisphere activity during language processing (2003), though these findings require replication. A 2003 treatment study by Neumann and colleagues demonstrated notable treatment effects. Prior to beginning treatment, stutterers showed mostly right

hemisphere activity in pre-central sensorimotor, frontal motor, parietal, right temporal, and limbic regions as well as the right insula. Widespread and bilateral activations were observed, however, in the frontal, temporal, and parietal regions after treatment (Neumann, Euler, von Gudenberg, Giraud, Lanfermann, Gall et al., 2003).

While fMRI has advanced to become a widely used form of functional brain imaging, it does have several disadvantages when used to image the brains of stutterers. Positron emission technology (PET) technology is another imaging option that offers a distinct advantage to fluency researchers for several reasons. First, the accuracy of PET data is not as susceptible to any movements made by subjects in the scanner as fMRI data. Additionally, PET offers a relatively noise-free research environment, a salient feature taken into account in speech studies where the noise associated with fMRI coils could be a confounding factor.

Measurement of CBF using PET technology was not a serious method of investigation, however, until the introduction of radioactive tracers. Ingham (2001) reported that early investigations incorporated somewhat archaic tracers, such as isotope injections directly into the carotid artery, and cameras. A 1980 study by Wood, Stump, McKeehan, Sheldon, and Proctor attempted to determine the effect of the drug haloperidol on the fluency of two right-handed adult stutterers. They used a non-tomographic procedure and Xenon as a tracer, scanning both subjects before and after receiving the drug. Results of the study showed atypical right hemisphere dominance during stuttering, which diminished after haloperidol reduced the subjects' stuttering. Left hemisphere dominance was then observed during fluent speech. This pattern led Wood and colleagues to conclude that stutterers possessed inadequate left cerebral

dominance for speech production. These results were limited, though; because the procedure was non-tomographic, the researchers could only distinguish CBF close to the surface of the brain.

Advances beginning in the mid-1970s solved this dilemma and enabled researchers to observe CBF throughout the brain. Using radioactive tracers that were injected into the bloodstream, tomographic representations of the annihilation of positron emissions from these tracers were developed and used to record these emissions as the tracer coursed through the brain (Ter-Pogossian, Phelps, Hoffman, & Mullani, 1975; Ter-Pogossian, Raichle, & Sobel, 1980). Soon afterwards additional types of tracers were developed, including F-18 deoxyglucose (FDG), ^{15}O, and $H_2{}^{15}O$ (Ingham, 2001). Both FDG and $H_2{}^{15}O$ PET allow the measurement of metabolic brain activity, by allowing recording of glucose uptake when behaviors are occurring. The $H_2{}^{15}O$ method is preferred because the scanning period is considerably shorter (40 seconds compared to the 45 minutes required using FDG methods).

A 1998 study played an important role in promoting PET as a viable and exciting technique to be used in stuttering research. In this study, Petersen, Fox, Posner, and Raichle performed $H_2{}^{15}O$ PET scans on their participants and discovered CBF activity in regions functionally correlated with speech and language. Specifically, they were able to demonstrate the areas of regional activations linked with passively viewing a word, hearing a word spoken, saying that word, and generating a verb from that word. This was an exciting breakthrough in speech research overall, as it suggested that PET could be used to further understand brain activity involved in speech. Particularly for stuttering research, it presented the possibility of using the new PET technology to assess both

stuttered and fluent speech (e.g., speech during fluency-inducing conditions) in order to isolate the neural regions functionally associated with stuttering. Following this discovery, numerous PET studies were performed by a variety of research groups, including the laboratories of Braun (Braun, Varga, Stager, Schulz, Selbie, Maisog et al., 1997), De Nil (De Nil, Kroll, & Houle, 2001; De Nil, Kroll, Kapur, & Houle, 2000; De Nil, Kroll, Lafaille, & Houle, 2003), Fox and Ingham (Fox, Ingham, Ingham, Hirsch, Downs, Martin et al., 1996; Fox, Ingham, Ingham, Zamarripa, Xiong, & Lancaster, 2000; Ingham, Fox, Costello Ingham, & Zamarripa, 2000; Ingham, Fox, Ingham, Xiong, Zamarripa, Hardies et al., 2004; Ingham et al., 1996), and Wu (Wu, Maguire, Riley, Fallon, LaCasse, Chin et al., 1995).

Synthesis of Results of PET Studies of Stuttering

Perhaps the most insightful information about the results and implications of these studies has come from a collection of reviews in this area. Several reviews and meta-analyses have synthesized knowledge about normal speech production (Fiez & Petersen, 1998; Indefrey & Levelt, 2000, 2004; Turkeltaub, Eden, Jones, & Zeffiro, 2002), and three have specifically focused on the disorder of stuttering (Brown, Ingham, Ingham, Laird, & Fox, 2005; Ingham, 2001, 2004).

Ingham's (2001) review sought to identify commonalities in the results of five PET studies, all of which had used a subtraction design. To determine similarities and difference in these studies, Ingham tabulated the label-reported activations and deactivations in each study. Results showed agreement in three of the five studies for

abnormal activations in the SMA and anterior insula, as well as deactivations in the auditory association areas.

A second tabular review by Ingham (2004) incorporated performance-correlation studies and also used more restrictive comparison data than the previous review (Brown et al., 2005). Results were similar to the 2001 analysis, finding partial overlap in the same regions, though greater agreement between studies was demonstrated when both the task and image-analysis methods were matched across the studies (Brown et al., 2005).

The interpretation of these two reviews, however, must be qualified. According to Laird and colleagues (Laird, Fox, Price, Glahn, Uecker, Lancaster et al., 2005), tabular meta-analyses have mediocre spatial precision and are thus weakened by the high variability with which brain regions are labeled by various research groups and in different studies. Coordinate-based, voxel-wise meta-analyses, however, offer a useful alternative by "deriving statistical whole-brain images of convergence across a corpus of studies" (Brown et al., 2005, p. 106). This type of meta-analysis had only been used to evaluate normal speech production (Turkeltaub et al., 2002) until Brown and colleagues used this method to evaluate stuttering in 2005.

In brief, Brown et al.'s (2005) review was a reanalysis of previously published data. Two activation likelihood estimation (ALE) meta-analyses were performed, using both activation and performance-correlation data. Three criteria were listed as necessary for inclusion in the review: coordinate-based analysis of data must have been used, most/all of the brain must have been imaged, and overt speech must have been used in at least part of the study (Brown et al., 2005). Following these guidelines, eight previous studies were included: six PET studies (Braun et al., 1997; De Nil et al., 2000; De Nil et

al., 2003; Fox et al., 1996; Fox et al., 2000; Ingham et al., 2004) and two fMRI studies (Neumann et al., 2003; Preibisch et al., 2003). Four studies were excluded; two failed to report spatial coordinates for regions in the brain (Van Borsel et al., 2003; Wu et al., 1995), one incorporated only partial brain scans (De Nil et al., 2001), and one relied upon data from covert speech alone (Ingham et al., 2000).

A preliminary point of interest in Brown et al.'s (2005) results involves the number of foci that were analyzed. Specifically, the number of analyzed foci for stutterers was more than twice the number of those analyzed in the controls (i.e., 154 compared to 73); in other words, stutterers show increased areas of activation and demonstrate a wider distribution of activated areas. This finding is especially notable considering that it can be corroborated by most studies in this literature (Brown et al., 2005).

Furthermore, the meta-analysis highlighted several remarkable areas. In terms of the brain areas argued to be important for normal speech production, Brown et al.'s (2005) results were very similar to previous meta-analyses of single-word reading (Fiez & Petersen, 1998; Indefrey & Levelt, 2000, 2004; Turkeltaub et al., 2002). These researchers contended, therefore, that a set of core areas exists which is critical for normal speech production, including the primary motor cortex, premotor cortex, SMA, frontal operculum, anterior insula, Rolandic operculum, cingulate motor area, basal ganglia (putamen and globus palidus), and lobule VI of the cerebellum.

In terms of disordered speech, the authors contend that the ability to compare these results with normal speech data is unprecedented and can offer readers unique insight into the pathology of stuttering. An important starting point to note is that the

series of core brain areas observed in the speech of stutterers was the same as that of the fluent controls, indicating that not only normal speech production but also stuttered speech is associated with activity in the aforementioned regions. Also, compared to Ingham's (2001; 2004) previous tabular reviews, the abnormal activations in the right frontal operculum, anterior insula, and cerebellum, as well as the deactivations in the right auditory association areas found previously, were validated in this analysis (Brown et al., 2005).

Three major differences in the speech of stutterers were noted. First, stutterers showed increased activation in lateral vocal-motor areas as compared to controls, especially in the right hemisphere, and decreased activation in auditory areas bilaterally. Second, there was a laterality shift to the right hemisphere in stutterers (e.g., a reduction of activity in left hemisphere areas and an increase in right hemisphere activities, or an overall "rightward shift in cerebral activation"), consistent with numerous pre-imaging studies of stuttering (Brown et al., 2005, p. 112). Finally, stutterers showed prominent overactivity in the medial motor structures: SMA, cingulate motor area, and cerebellar vermis (lobules VI/III). This finding of abnormal SMA activity is consistent with Ingham's (2001) conclusions. With these unique characteristics in mind, Brown and colleagues expound on what they describe as three neural signatures of stuttering.

They emphasize the first significant marker, the presence of overactivations of the right frontal operculum and anterior insula, for numerous reasons. Primarily, these activations were unlike the other lateral motor areas because the activity was solely in the right hemisphere and was unique to the stutterers. Activations in this area were much higher during stutter-filled solo-reading versus stutter-free chorus-reading in Fox et al.'s

(1996) PET study. A more intriguing finding by Neumann and colleagues in their treatment study indicated that activations in this area were present before treatment but were eliminated afterwards (Neumann et al., 2003). It has been suggested that the production and perception of vocal fundamental frequency is mediated to some degree by these areas (Brown et al., 2005), thus abnormal activations in this region may produce deviant phonological processing in stutterers.

Brown et al.'s second proposed neural marker is reduced brain activity in auditory areas during vocalization, a much-replicated finding throughout the imaging literature. This is a notable suggestion, as the control group of this meta-analysis as well as all previous meta-analyses of vocal production have shown prominent and typically bilateral activations during speech (Brown et al., 2005). Because Brown et al.'s analysis did not incorporate reports of deactivations or negative correlations from the reviewed studies, they recommend an overview of the literature to define and defend this assertion.

A 1996 study was the first to show clear reductions in superior temporal lobe activations and even deactivations during reading (Fox et al., 1996). Following this, numerous studies revealed the absence of, or a decrease in, bilateral activations in auditory areas in stutterers during moments of stuttering (Braun et al., 1997; De Nil et al., 2000; Stager, Jeffries, & Braun, 2003; Van Borsel et al., 2003). Additionally, negative correlations were shown between auditory activations and: stuttering (Braun et al., 1997); stuttering rate in males (Fox et al., 2000) and females (Ingham et al., 2004); and stuttering severity (Neumann et al., 2003). In fact, the only study to indicate no auditory effect in stutterers was performed by De Nil and colleagues in 2003; the controls in this study did not demonstrate auditory activations during overt reading similar to that of

controls in previously mentioned studies, however, indicating that the data from the stuttering subjects may have been similarly difficult to interpret (Brown et al., 2005). The cumulative evidence not only points to an auditory inhibitory effect in stutterers but also indicates that this effect is amplified by the severity of stuttering and improved by FICs and even treatment. Considering this convergence of imaging evidence, the auditory inhibitory effect may be one of the most distinctive indicators of stuttering presently known (Braun et al., 1997; Ingham, 2001). Brown et al. (2005) couple this effect with the previously mentioned idea of atypical phonological processing and also suggested that these findings may indicate a disrupted functional connection between the motor and auditory areas during speech planning in stutterers.

Finally, Brown et al. (2005) suggested that stutterers show activation in the vermal portion of the cerebellar Lobule III. Previous studies have showed activity in lobules V (Fiez & Petersen, 1998) and VI (Brown et al., 2005; Turkeltaub et al., 2002) for overt vocalizations. Activations in lobule III have been demonstrated in several studies and seem to be unique to stutterers. For example, data from Fox et al. (1996) showed activity in the vermis of lobule VI during stutter-free chorus reading, similar to data from non-stuttering controls, but activity shifted to the vermis of lobule III during stutter-filled solo reading. Similarly, activity in lobule III was not demonstrated by the controls of a 1997 study by Braun and colleagues nor was it seen in the fluent speech of stutterers, though it was active during stutter-filled speech. A treatment study also showed no activations in lobule III for the controls, though activity in this region was demonstrated by the stuttering subjects and disappeared post-treatment (De Nil et al., 2003).

Implications of Brain Imaging Studies of Stuttering

Overall, Brown et al.'s (2005) meta-analysis provides a framework for the neurophysiologic study of the relationship between brain and behavior. By choosing a specific behavior (i.e., speech) and investigating its neurological patterns during both normal and abnormal function, Brown and colleagues established an ideal method for the study of brain and behavior. Comparison of the neurophysiologic markers of normal function with those of abnormal function is arguably an elegant way to ascertain the specific patterns and regions involved in neural dysfunction.

Furthermore, the possibility that this body of research may have identified neural markers of stuttering is an exciting move forward in our understanding of this disorder. While the prospect of four neural markers of stuttering is a promising development, no single study performed previously or since has found these, *and only these*, four neural markers proposed by Brown and colleagues (2005). Thus it seems that stutterers are not as homogenous a group of people as they might seem. And herein lies a fundamental problem – if the results of Brown et al. (2005) reflect a group of stutterers, which group do they represent? As of now, there is not enough evidence to provide a clear answer. Consequently, it is difficult to maintain that these findings reflect a single group of stutterers, let alone an individual stutterer. Replication of their methods and results is an obvious need.

Another important issue involves the clinical nature of speech language pathology. If specific knowledge regarding the neurophysiologic characteristics is to become useful to practitioners in the discipline, imaging studies must lead to more than a list of atypical activations in the brains of groups of stutterers. Even suggestions about

which areas might change with treatment are not directly useful to the development or use of stuttering treatment.

Ideally, imaging technology could be utilized with individual stutterers to identify the individual's aberrant neural system and use this knowledge to design treatments aimed at modifying this system in order to enhance fluency (Ingham, 2004). For example, researchers could use imaging of individuals to track neurological changes before, during, and after behavioral treatment so as to determine whether the treatment protocol is effective. Moving from studies of groups to individual clients, however, involves numerous complications. Among the most important are several methodological issues, discussed below.

Image Subtraction

One of the complexities inherent in attempting to identify the neural signature of any particular behavior is that the brain is always active, thus making it difficult to localize task-related brain activity. Therefore, many of the initial neuroimaging studies employed what is known as the "subtraction design," intended to filter out irrelevant brain activity in order to highlight activity in regions of interest specific to the question at hand. Following this design, a participant is first scanned during a period of rest in order to determine their base rate of, for example, CBF. Afterwards, scans are completed during various activation conditions (e.g., reading out loud, speaking a monologue, etc.). To identify the significantly activated or deactivated areas in these conditions, the initial base rate scans are subtracted from scans from each condition in order to clearly portray areas functionally associated with each task. For example, an individual may complete scans during a period of rest and while reading aloud. The neural activity from the

baseline resting scan is then subtracted from the activity recorded during the reading scan, thus removing any activity associated with rest and illuminating the activity functionally associated with reading aloud. From this point, the conditions are then compared to one another in order to determine variations in regional activation patterns, and thus enable identification of brain activity that may be functionally associated with a specific task, such as reading aloud.

The conclusions reached through subtraction design are not entirely accurate, however, because of the "pure insertion" problem associated with this design. In short, this experimental paradigm assumes that only one "pure" variable differentiates the two conditions being compared; or, in other words, that the conditions are identical in every way except for one distinguishing variable (Grabowski & Damasio, 2000; Ingham, 2001, 2003; Petersen, van Mier, Fiez, & Raichle, 1998). Fox et al. (2000) astutely point out that conditional contrasts assume that an investigator is able to isolate the desired event into only one condition, which in reality is quite a rare feat. For instance, a researcher would need to isolate events of stuttering into only one condition, say during spoken monologue, and eliminate them from all other spoken tasks. Stuttering is simply not able to be predicted and controlled for in that manner, however. Thus, conclusions made in stuttering research using this design are at risk of being inaccurate and misleading.

Other experimental designs have emerged that offer a more suitable and accurate means of discovering brain activities that are functionally associated with stuttering. One such method, performance correlation analysis, was first introduced by Silbersweig and colleagues (1995) in a study designed to map the brain locations essential to auditory hallucinations in schizophrenia. This method operates upon the tenet that the intensity of

brain activations can be correlated with the frequency of use of the neural elements being observed during imaging. The implication for stuttering would suggest that specific areas that change concurrently with stuttering frequency might be identifiable (Ingham, 2003). Braun and colleagues (1997) were the first to use this method within the realm of stuttering research and have been followed by numerous other researchers in the field (Fox et al., 2000; Ingham et al., 2004; Stager et al., 2003).

Image Averaging

The common method of data analysis presently used is a combination of not only image subtraction but also intersubject image averaging. The need for this combination of methods arose primarily because of the need for measurement accuracy that accompanied the shift from studying very basic movements or sensory activity to studying other higher-order, nonprimary areas such as those involved in speech. These areas activate with a much lesser intensity than lower-order areas (e.g., primary sensory cortex) (Fox, Mintun, Reiman, & Raichle, 1988), making it difficult to precisely measure and map any significant changes in activation for complex higher-order activity.

As an early solution to this problem, Fox and colleagues borrowed an idea known as signal averaging, which is widely used in studies of a temporal nature (i.e., EEG, MEG, etc.) to reduce measurement noise (Fox et al., 1988). The logic of signal averaging assumes that background noise accumulated over several trials will cancel, while constant focal activity will aggregate, and thus task-specific neural activity would be more readily distinguishable; in other words, the signal-to-noise ratio would improve (Fox et al., 1988). Their seminal study initiated this technique as a viable option to improve activation measurements in spatial studies.

Image Standardization

Successful use of image averaging, however, requires that each image be anatomically standardized (Fox et al., 1988). Standardization is necessary to correct for individual differences in brain size and shape as well as any variations in the orientation of each brain slice. The need for highly accurate standardization was an issue, however, since the process of standardization often caused image warping. There are several physical, imaging, and statistical methods to achieve such standardization. In brain imaging research, the most common by far has been the use of a brain atlas. The stereotaxic atlas created by Talairach and Tournoux in 1988 is considered the most universally used atlas in functional imaging (Brett, Johnsrude, & Owen, 2002). This innovative atlas introduced three important developments. First, the atlas describes a standard brain and includes anatomical and cytoarchitectonic labels. Second, a spatial transformation is provided to match one brain to another. Perhaps most importantly, a coordinate system was introduced to use in pinpointing specific brain locations relative to anatomical markers in three dimensions (e.g., *x*, *y*, and *z* coordinates), and also delineated where each dimension would begin and end (Brett et al., 2002). Therefore, when using this atlas it is possible to standardize brain images from a number of individuals, as well as from one individual in a variety of tasks, by discussing points in a three dimensional space relative to three central axes in the brain.

Present Purpose

The methodological issues discussed above (i.e., subtraction design, image averaging and standardization) raise problems for the scientific interpretation and clinical

use of the results from group studies of stutterers. The current common practice in fluency research using brain imaging, however, is to average individual results across participants and to discuss findings in terms of group results. Yet this practice seems premature, as the homogeneity of stutterers as a group is yet to be determined. Additionally, without evidence that individual stutterers resemble groups of stutterers in terms of neural activity, the utility of this data is questionable; it remains unclear whether the current use of imaging technology in studies of stuttering has scientific and clinical relevance when dealing with individual stutterers.

A predominant and fundamental need in the field of fluency research is a basic understanding of the neural activity of both individuals as well as groups of people who stutter. This knowledge will then guide future endeavors, such as that demonstrated by Brown et al. (2005), to determine the core neural characteristics of people who stutter. From a clinical standpoint, a salient drawback of group studies is that they generally offer implications for groups rather than individuals who stutter. While the numerous studies discussed previously have shown convincing evidence of aberrant neural involvement in groups of stutterers, this group data is simply inadequate for developing treatments aimed at individuals who stutter. Thus it is essential that patterns of neural activity in individuals who stutter, as well as in groups of stutterers, be determined, if brain imaging research is to have meaningful clinical implications. The purpose of this present study, therefore, was to compare the results of a small number of individuals who stutter with results from previous group studies. The general goal was to determine if any similarities and differences in neural activation and deactivation patterns could be identified between

individuals, as compared to groups of individuals, who stutter. The following questions were addressed:

(i) What pattern of neural activity occurs in individuals who stutter, and does this pattern resemble the activity reported for groups of stutterers?

(ii) Are certain neural activations task-dependent (e.g., do they occur only in the monologue or oral reading condition)?

(iii) Do individual stutterers demonstrate reduced neural activity, even deactivations, in auditory areas in ways similar to groups of stutterers?

(iv) Does gender influence neural activity?

CHAPTER 2: METHODS

The analysis completed for this thesis was based on imaging data from three adults. The means by which these data were originally acquired are described first. Following that description, the methods for analysis of individual participants are described.

Original Data Acquisition

Participants

Data for this study was collected from three participants, two dextral females (ages 54 and 56) and one dextral male (age 58), all sharing a history of developmental stuttering. Group data from previous group studies of males and females (Brown et al., 2005; Ingham et al., 2004) were obtained for comparative purposes. Informed consent was given by all participants in accordance with the regulations of the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

Image Acquisition and Analysis

Each individual completed five PET imaging sessions, each separated from the next by a span of several weeks. All imaging was performed according to FDA standards on a Siemens/CTI HR+ PET scanner. Each session was comprised of 6 scans, two during each of the three conditions: eyes closed rest (Rest), oral paragraph reading (Read), and monologue (Mon). Reading material used during the reading condition was presented to the participants visually via an LCD monitor. PET images for all subjects were corrected for motion within each session and co-registered across sessions and with MRI images in

order to place them in standard space relative to the Talairach atlas (Talairach & Tournoux, 1988). A more detailed description of this methodology is reproduced in relevant paragraphs from Ingham (2006) in Appendix A.

The Present Analysis

Speech Measurements

Speech performance data were derived from audiovisual recordings obtained during each of the nine PET scans. Recordings were scored independently by a main judge of stuttering and one additional speech language pathology graduate clinician. Data were collected using the Stuttering Measurement System program (Ingham, Bakker, Kilgo, & Moglia, 1999).

Reliability

Reliability checks were performed on all speech performance data. Interjudge reliability for the percent of syllables stuttered (%SS) was assessed by having the primary investigator and graduate clinician score all tasks in each condition. Intrajudge reliability for %SS was assessed by having both the primary investigator and graduate clinician re-score all tasks in each condition. These data are discussed in detail in the results section and shown in a tabular form.

Individual Neural Activity

The neural activity of each individual was analyzed to determine any significant activity (i.e., activation and deactivation patterns) in 19 ROIs throughout the brain. The

amount of neural activity was determined by measuring the number of contiguous voxels (image volume elements, measuring 2 x 2 x 2 mm) in each cluster of activity. Only clusters of 15 or more voxels were included in analysis. In order to perform comparative analyses with group data, 18 regions incorporated in the present analysis were chosen from those included in the Brown et al. (2005) ALE meta-analysis. The other region incorporated in the analysis was the middle temporal gyrus, so as to thoroughly investigate the temporal lobe activity of the individuals. All summed voxel values for each ROI during both tasks and for both type of activity is displayed in tabular form in Appendix B.

Each of the 20 regions was classified as either significantly activated ($P < 0.05$, $Z > 0$), significantly deactivated ($P < 0.05$, $Z < 0$), or neither. When both types of activity were present in a certain region, either the activations or deactivations had to be equal to or greater than 90 percent of the total neural activity in order to be included in analysis (Ingham, personal communication). This rule was used to separate genuine regional activations or deactivations from those which were indistinct secondary to both types of activity being present in the region.

Correlations

In addition to the region by region analyses, obtained data were further assessed using correlations for each subject and for all subjects combined. The dependent variable for all correlations was number of voxels significantly activated or deactivated. Pairs of variables to correlate were defined by hemisphere (left versus right), task (oral reading versus monologue), and activations versus deactivations. These analyses used rank order

correlations (Pearson product-moment correlation for ranks) to eliminate problems associated with positively skewed data.

Individual versus Group Comparisons

Activation and deactivation data from previously published group studies (Brown et al., 2005; Ingham et al., 2004) were compared with individual results from the present analysis. Qualitative measures, including visual analysis of data charts, were employed to compare the two sets of data.

CHAPTER 3: RESULTS

Stuttering Frequency Data

As expected, all three participants displayed stuttered speech in each of the two speaking conditions. Table 1 shows the %SS for each participant during both conditions as well as each participant's mean %SS per condition. Mean %SS ranged from 7.8 – 38.58 during the monologue condition and 6.61 – 26.78 during oral reading. Subject 1 displayed the highest %SS in both conditions, with a mean of 38.58 %SS during the monologue and a slightly lower mean of 26.78 %SS during oral reading. Subject 2 demonstrated a lower frequency of stuttering events and had very similar patterns of stuttering during both conditions, with a mean of 10.13 %SS during the monologue and 10.19 %SS during oral reading. Subject 3 showed the lowest %SS of the three participants, with a mean of 7.80 %SS during the monologue and 6.61 %SS during oral reading.

Reliability

Comparison of the stuttering judgments made by the two judges demonstrates suitable interjudge reliability. Table 2 lists the %SS counts of both judges and the whole number discrepancy between each count. Most of the frequency counts differ by less than 1 %SS, with only four differing by 1-2 %SS. In fact, two of the twelve counts were

Table 1. Stuttering frequency data (reported in percent syllables stuttered (%SS)) for all speaking tasks for all participants.

	MONOLOGUE 1	MONOLOGUE 2	MONOLOGUE MEAN	READING 1	READING 2	READING MEAN
Subject 1	34.48	42.68	38.58	26.72	28	26.78
Subject 2	11.72	8.54	10.13	11.54	8.84	10.19
Subject 3	4.80	10.79	7.80	7.80	5.41	6.61

Table 2. Interjudge reliability for stuttering frequency data (%SS).

CONDITION	MAIN JUDGE	RELIABILITY JUDGE	DIFFERENCE
Sub1: Mon 1	34.48	35.16	0.68
Sub1: Mon 2	42.68	42.17	0.51
Sub1: Read 1	26.72	25.64	1.08
Sub1: Read 2	28	28	0
Sub2: Mon 1	11.72	10.26	1.46
Sub2: Mon 2	8.54	8.50	0.04
Sub2: Read 1	11.54	10	1.54
Sub2: Read 2	8.84	9.29	0.45
Sub3: Mon 1	4.80	4.26	0.66
Sub3: Mon 2	10.79	9.72	1.07
Sub3: Read 1	7.80	7.80	0
Sub3: Read 2	5.41	4.76	0.65

Table 3. Intrajudge reliability for stuttering frequency data (%SS).

CONDITION	MAIN JUDGE			GRADUATE CLINICIAN		
	1st Count	2nd Count	Difference	1st Count	2nd Count	Difference
Sub1: Mon 1	34.48	37.35	2.87	35.16	31.76	3.4
Sub1: Mon 2	42.68	42.17	0.51	42.17	41.28	0.89
Sub1: Read 1	26.72	26.72	0	25.64	25.22	0.42
Sub1: Read 2	28	28.21	0.21	28	27.36	0.64
Sub2: Mon 1	11.72	8.87	2.85	10.26	6.3	3.96
Sub2: Mon 2	8.54	5.52	3.02	8.50	5	3.5
Sub2: Read 1	11.54	11.38	0.16	10	9.84	0.16
Sub2: Read 2	8.84	9.84	1	9.29	6.57	2.72
Sub3: Mon 1	4.80	2.96	1.84	4.26	2.53	1.73
Sub3: Mon 2	10.79	10.49	0.30	9.72	10.42	0.7
Sub3: Read 1	7.80	6.52	1.28	7.80	7.14	0.66
Sub3: Read 2	5.41	4.79	0.62	4.76	4.73	0.03

identical. It is notable that the two judgments are very reliable even for Subject 1 who demonstrated high stuttering rates.

Intrajudge reliability measures for stuttering frequency were also conducted for the main stuttering judge and the graduate clinician for each of the twelve speaking tasks. As can been seen in Table 3, intrajudge reliability can also be considered suitable for both judges. Half of the counts differed by less than 1 %SS, with four counts differing by 1-2 %SS, three counts differing by 2-3 %SS, and four counts differing by 3-4 %SS.

Neural Activity during Oral Reading

In terms of the activations and deactivations overall, during oral reading (as compared with rest), there was no distinct pattern across the three subjects. Figures 1 & 2 show the neural activity for all three individuals during this task. Colored bars in each figure represent the three participants' number of significantly activated voxels in all analyzed regions; subject one is denoted with white bars, subject two with grey bars, and subject three with black bars.

Activations

All three subjects showed significant activations during oral reading in three of the sixteen regions; that is, activations in the STG and anterior insula of the LH and in the vermis VI of the RH. Two of the three subjects showed significant activations in the SLPrM, frontal operculum, rolandic operculum, and lobule VI and the vermis VI of the LH. At least one of the three individuals displayed activations in the anterior cingulate

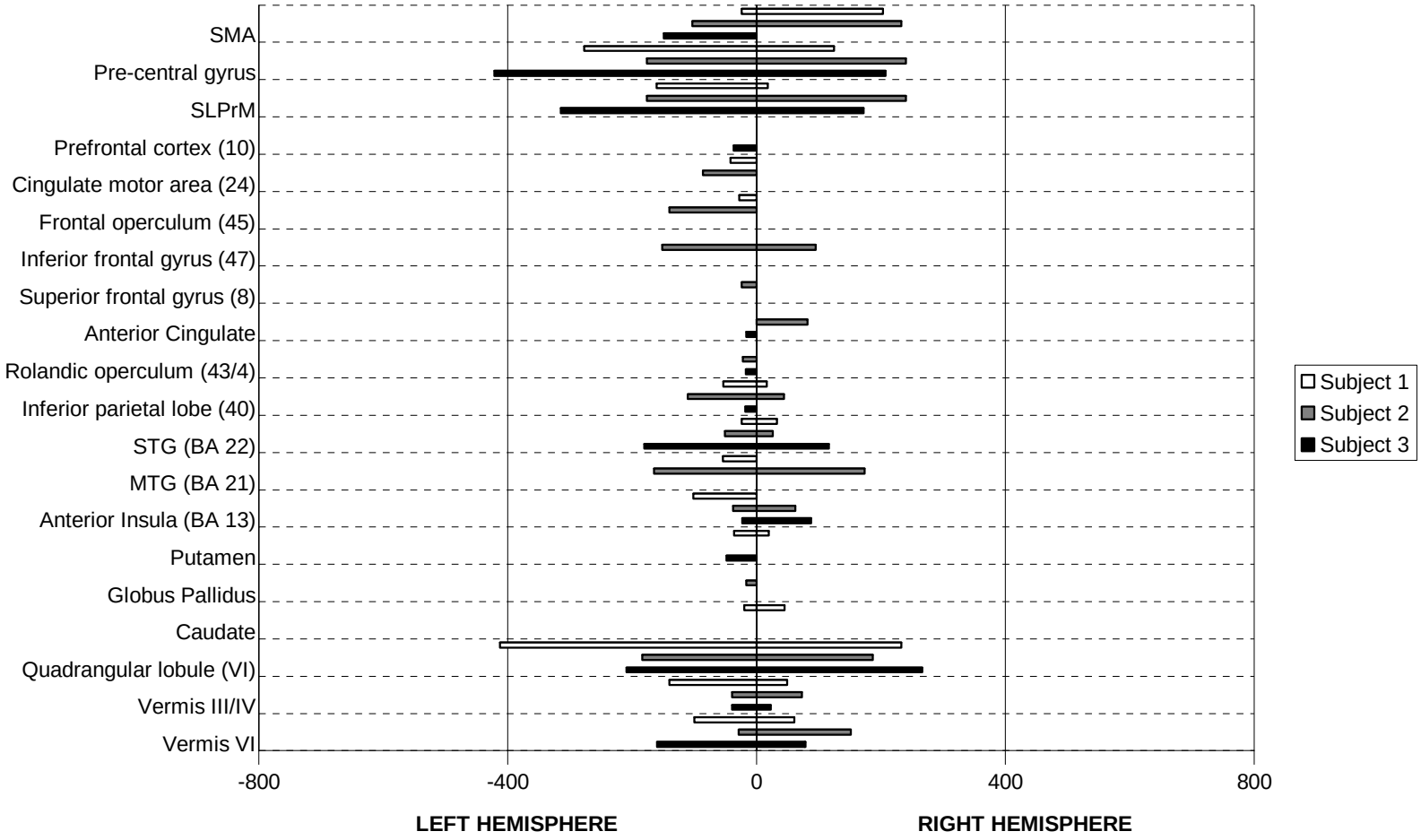

Figure 1. The number of significantly activated voxels that occurred for each of the three subjects during the oral reading (r-ECR) condition.

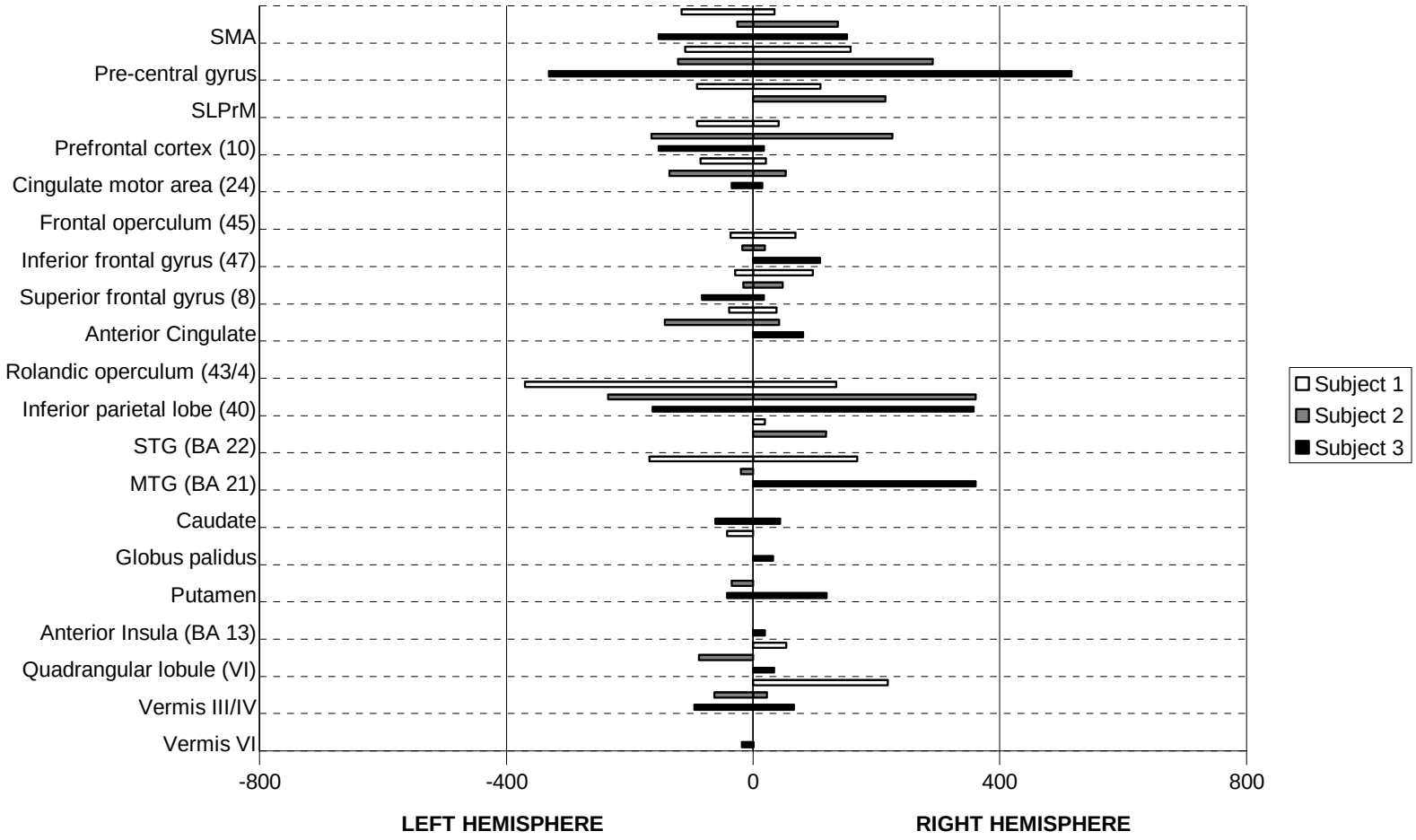

Figure 2. The number of significantly deactivated voxels that occurred for each of the three subjects during the oral reading (r-ECR) condition.

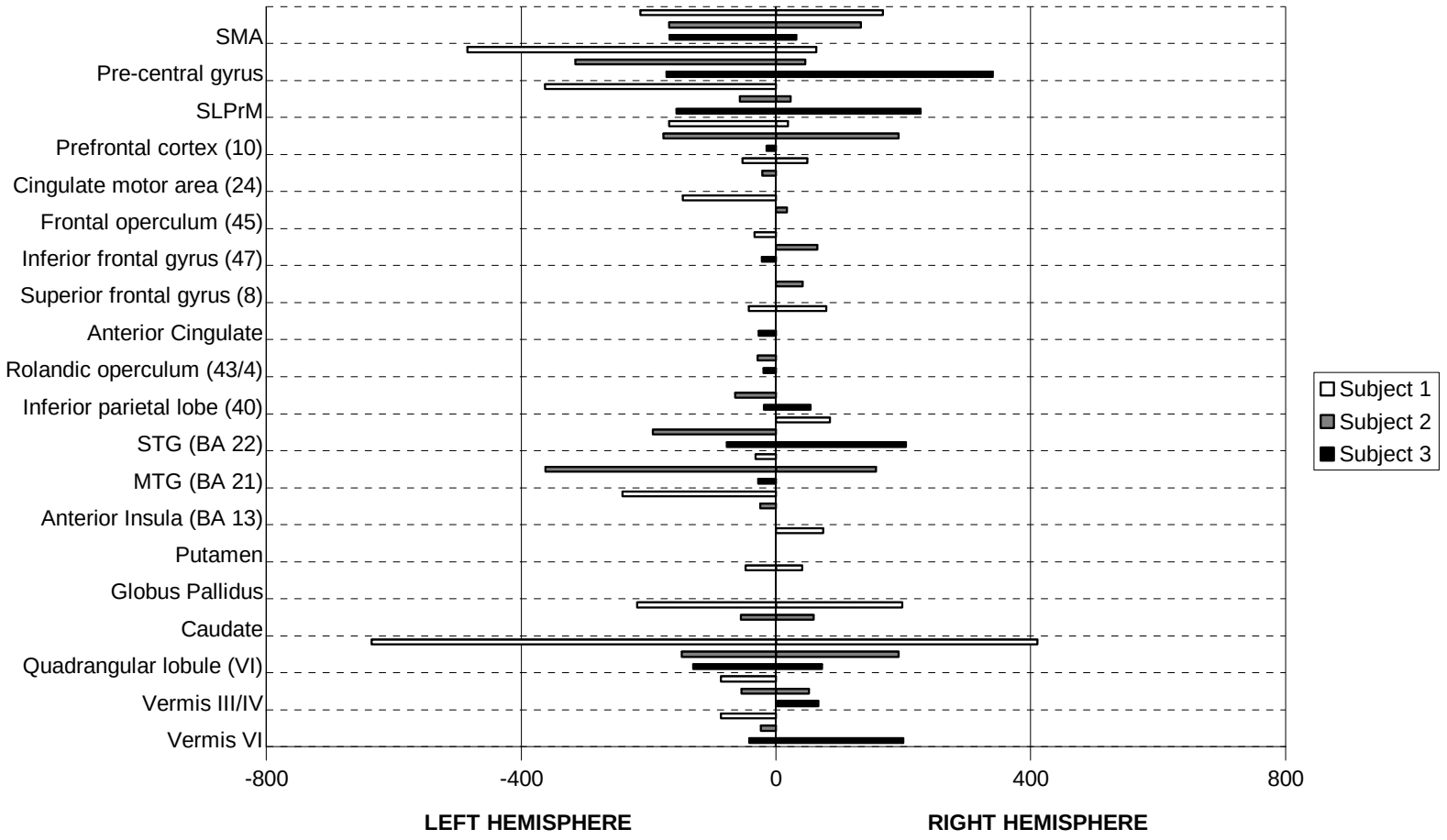

Figure 3. The number of significantly activated voxels that occurred for each of the three subjects during the monologue (m-ECR) condition.

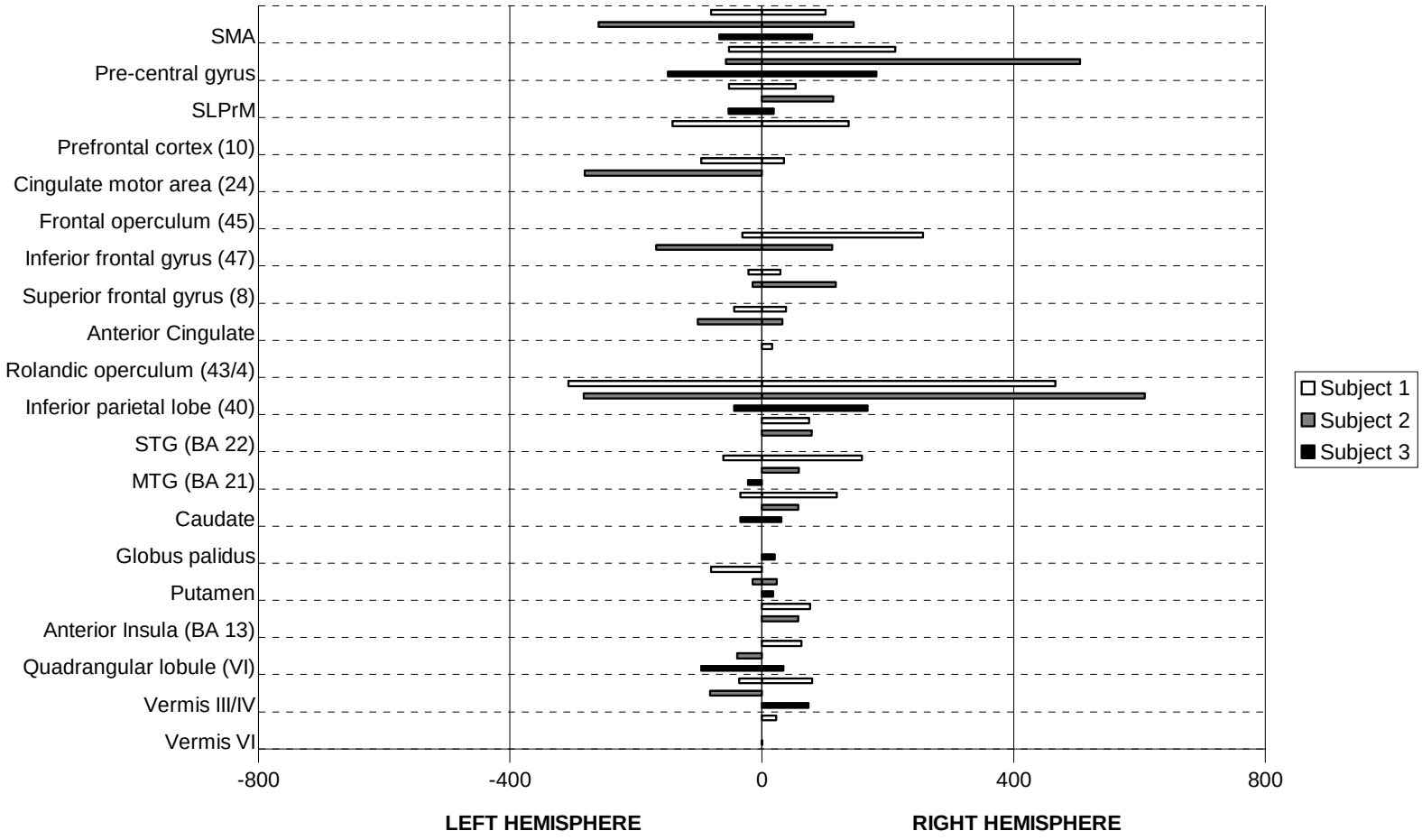

Figure 4. The number of significantly deactivated voxels that occurred for each of the three subjects during the monologue (m-ECR) condition.

and the vermis III/IV of the LH as well as in lobule VI, the anterior insula, middle and superior temporal gyri, and SLPrM of the RH.

Deactivations

All three participants showed significant deactivations during oral reading in three frontal regions of the sixteen regions overall, the prefrontal cortex, cingulate motor area, and the superior frontal gyrus of the RH. The MTG, anterior cingulate, and inferior frontal gyrus of the RH were deactivated in two of three subjects. The cingulate motor area, inferior frontal gyrus, anterior cingulate, and inferior parietal lobe of the LH and the SMA and inferior parietal lobe of the RH were deactivated in at least one participant.

Neural Activity during Monologue

The three individuals did not exhibit an overall pattern of activations and deactivations during the monologue condition (as compared with rest), instead demonstrating indiscriminate activity much like that shown during the oral reading task. The same 90% rule (Ingham, personal communication) used to analyze activity in oral reading was used in analysis of activity during the monologue condition. Figures 3 & 4 show the neural activity for all three individuals during this task. Colored bars represent each participant's significant number of significantly activated voxels in all analyzed regions in the same manner as Figures 1 & 2.

Activations

Vermis III/IV of the LH was the only region significantly activated during the monologue tasks in each individual. Two of the three participants showed significant LH

activations in the prefrontal cortex, rolandic operculum, superior temporal gyrus, and anterior insula. One of the three subjects demonstrated significant activations in the precentral gyrus, SLPrM, frontal operculum, inferior frontal gyrus, anterior cingulate, MTG, and lobule VI of the LH and in the SLPrM, prefrontal cortex, frontal operculum, STG, all cerebellar regions of the RH.

Deactivations

No regions were shown to be deactivated during monologue tasks in all three individuals in either hemisphere. Two of the three individuals showed significant deactivations in the superior frontal gyrus of the LH and the inferior parietal lobe and anterior insula of the RH. At least one of the three participants showed deactivations in the cingulate motor area, inferior frontal gyrus, anterior cingulate, and inferior parietal lobe of the LH and in the precentral gyrus, SLPrM, inferior frontal gyrus, superior frontal gyrus, anterior cingulate, rolandic operculum, STG, MTG, and the vermis VI.

Task-Dependent Activity

The individual data described above is demonstrated in a different way in Figures 5-7, which show a comparison of oral reading and monologue activity for each of the three individuals. The white and black bars in these figures represent the number of significantly activated and deactivated voxels in all analyzed regions during the monologue condition, while the texturized white and black bars represent the number of significantly activated and deactivated voxels in all analyzed regions during the oral reading condition. These are then summarized for all points in Table 4.

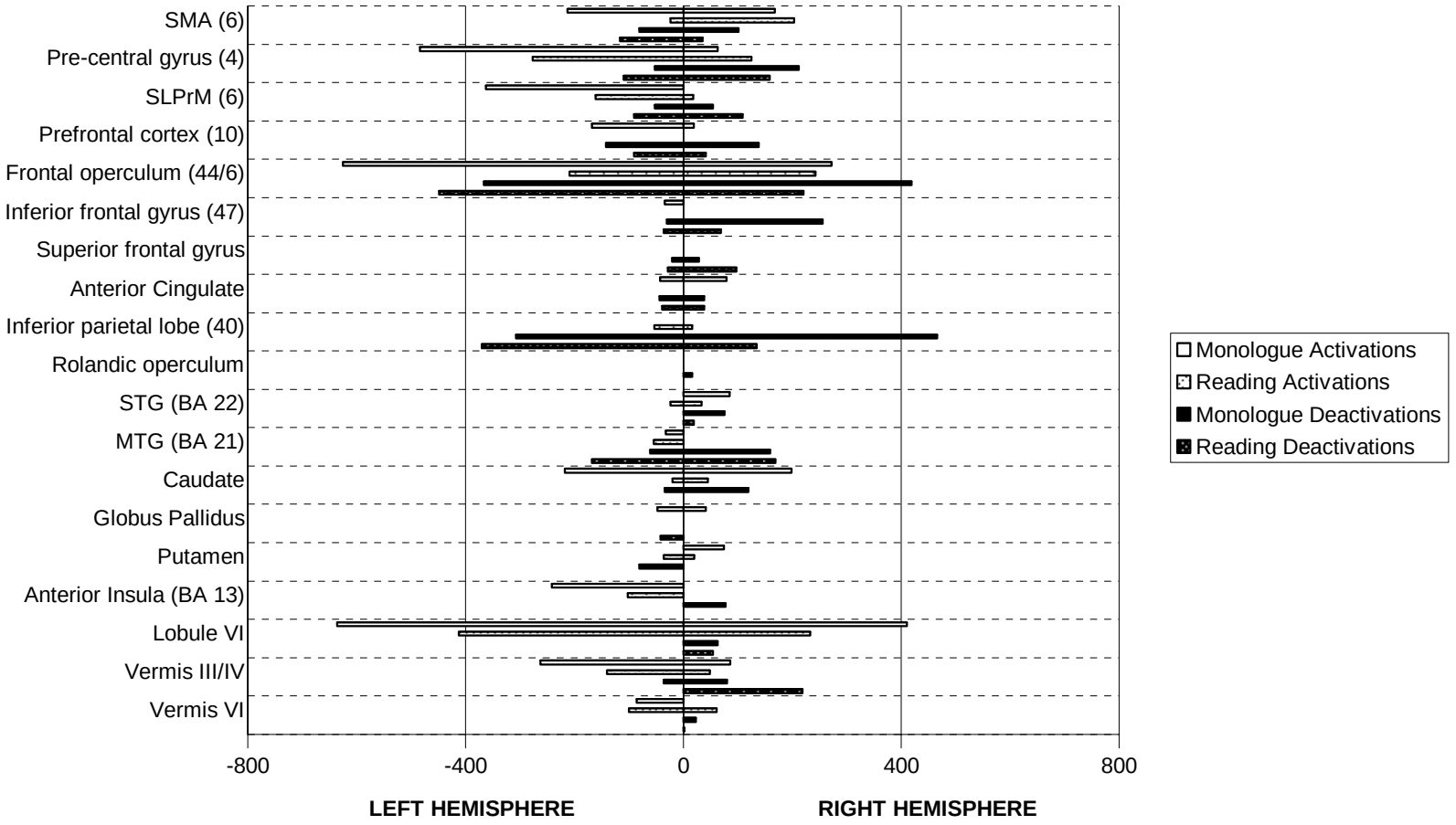

Figure 5. Comparison of the significantly activated and deactivated voxels that occurred during the monologue and reading tasks for Subject 1.

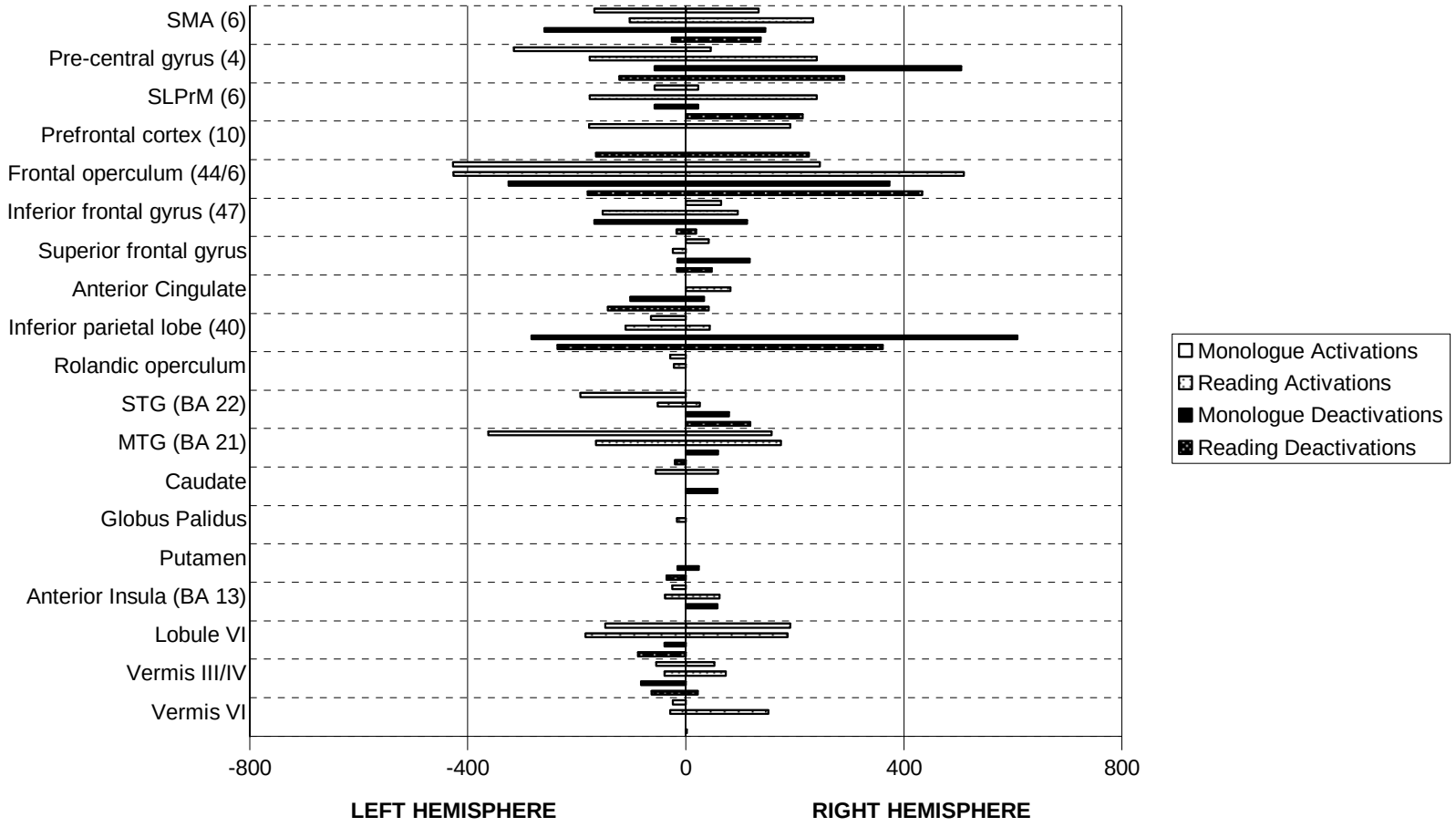

Figure 6. Comparison of the significantly activated and deactivated voxels that occurred during the monologue and reading tasks for Subject 2.

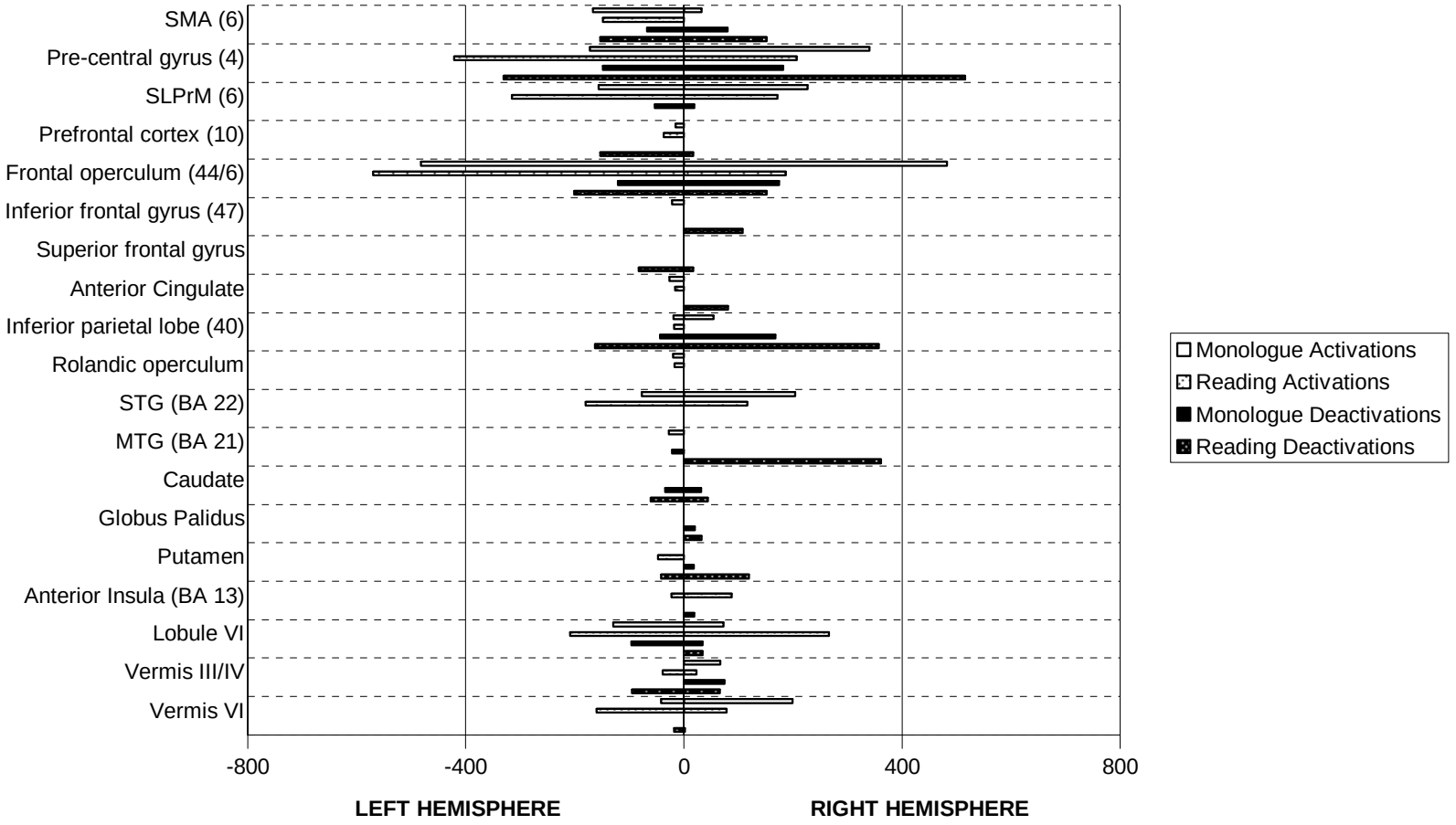

Figure 7. Comparison of the significantly activated and deactivated voxels that occurred during the monologue and reading tasks for Subject 3.

Table 4. Neural regions showing significant task-dependent activity

		MONOLOGUE						READING					
Lobe	Region (BA)	Subject 1		Subject 2		Subject 3		Subject 1		Subject 2		Subject 3	
		L	R	L	R	L	R	L	R	L	R	L	R
Frontal	Supplementary motor area (6)												D
	Precentral gyrus (4)	A			D								
	Premotor cortex (6)		D										
	Prefrontal (10)			A	A	A		D	D	D	D		D
	Inferior frontal gyrus (47)					A							
Parietal	Rolandic operculum (43/4)						D						
Temporal	Superior temporal gyrus (22)				D								
	Middle temporal gyrus (21)			A							A		
Sub-lobar	Anterior insula		D		D						A		
Cerebellum	Vermis III/IV				A			A					
	Vermis VI		D										

A indicates significant activation; D indicates significant deactivation.

Each participant is listed with task-dependent activity marked with ‘A’ to signify activations and ‘D’ for deactivations next to the corresponding neural region. No general pattern was evident in the activity of ROIs activated in only one of the two conditions. Activity during both tasks was seen sporadically across hemispheres, across 11 of the 17 included areas, and in all lobes except for the anterior cingulate of the limbic lobe. Significant task-dependent activity was most commonly seen in only one of the three participants during both conditions. One exception was seen, however, in the prefrontal cortex. At least one hemisphere was significantly activated in two of the three participants during the monologue condition; all three individuals showed significant deactivations during the reading condition, with two of the three displaying bilateral deactivations.

Neural Activity in Auditory Areas

Left hemisphere activity in the STG was clearly evident; two of the three individuals showed significant activations during the monologue condition and all three showed significant activations during the oral reading condition. Additionally, no LH deactivations were seen in either condition. Right hemisphere activity was less robust, with only one of the three participants showing significant activations. Deactivations in the RH were minimal; one individual showed significant deactivations during the monologue condition. No significant deactivations during the oral reading condition were noted. Bilateral activations were shown in one of the three participants.

Correlations

All positive and negative correlations between the three individuals' data and for the participants as a group are shown in tabular form in Appendix C. The correlations for all three subjects as a group between oral reading and monologue, in the left hemisphere and right hemisphere, and during activations and deactivations are displayed in Table 5 and are discussed in detail below.

Correlations between Oral Reading & Monologue			**Correlations between Left Hemisphere & Right Hemisphere**			**Correlations between Activations & Deactivations**		
	LH	RH		OR	MON		OR	MON
Activations	0.53	0.40	Activations	0.57	0.47	Left Hemisphere	0.04	0.16
Deactivations	0.35	0.40	Deactivations	0.41	0.53	Right Hemisphere	-0.02	0.23

Table 5. Correlations for the group average of all three subjects. OR = oral reading, MON = monologue.

Relationships between Oral Reading and Monologue

Left hemisphere activations during oral reading were moderately correlated with left hemisphere activations during monologue, for the three participants combined (r = .53) and for each individual (r = .59, .41, .66). Left hemisphere deactivations during oral reading showed less of a relationship with left hemisphere deactivations during monologue than was evident for the activations (r = .35 for the group and .04, .73, and .30 for individuals). A similar pattern was obtained in the right hemisphere both for activations and for deactivations. Right hemisphere activations during oral reading were moderately correlated with right hemisphere activations during monologue for the group as a whole (r = .40), but with considerable variability across individuals (r = .01, .35, .80). Right hemisphere deactivations during oral reading, similarly, were moderately

correlated with right hemisphere deactivations during monologue for the group (r = .40) but not for all individuals (r = .16, .57, .55).

Relationships between Left Hemisphere and Right Hemisphere

Left hemisphere activations during oral reading were moderately correlated with right hemisphere activations during oral reading, and left hemisphere activations during monologue were moderately correlated with right hemisphere activations during monologue, for the three participants combined (r = .57 in oral reading; r = .47 in monologue). In both cases, however, there were notable differences across participants (r = .16, .68, and .79 in oral reading; r = .27, .46, .69 in monologue). A similar pattern was obtained for deactivations: Left hemisphere deactivations during oral reading were moderately correlated with right hemisphere deactivations during oral reading, with variability across participants (all r between .26 and .54; see Appendix C), and left hemisphere deactivations during monologue were moderately correlated with right hemisphere deactivations during monologue, again with variability across participants (all r between .33 and .73; see Appendix C).

Relationships between Activations and Deactivations

During oral reading, left hemisphere activations were not related to left hemisphere deactivations (r = .04 for the group; r = -.14, .07, and .21 for individuals), and right hemisphere activations were not related to right hemisphere deactivations (r = -.02 for the group; r = -.11, .26, -.17 for individuals). A similar lack of relationship was obtained between activations and deactivations during monologue for the group

(r = .16 for the left hemisphere and .23 on the right) and for Participants 1 and 2. For Participant 3, however, activations and deactivations were moderately correlated during monologue in the left hemisphere (r = .62) and in the right hemisphere (r = .52).

Individual Data Compared to Group Data

To begin to relate individual data to previously published group data, a comparison of individual and group activations is shown in Table 5. Data for each participant as well as the group data described in Brown et al. (2005) is listed for the 20 analyzed regions. In four out of the twenty ROIs, all three subjects showed activations matching those shown in Brown et al.'s meta-analysis. Specifically, the three individuals displayed bilateral activations in the precentral gyrus and frontal operculum, LH activations in the SMA, and RH activations in the premotor cortex. In six of the remaining regions, individual activations matched the Brown et al. (2005) group data with one exception: at least one of the three subjects did not demonstrate activity in one of the two conditions. For example, the LH activation in the prefrontal cortex shown in the Brown et al. (2005) group was replicated in only the monologue condition in two of the three individuals. This pattern of activity was also seen in the inferior parietal lobe, superior temporal gyrus, and all regions of the cerebellum. Brown et al. (2005) also reported RH activations in the inferior and superior frontal gyri, LH activations in the anterior insula, and bilateral activations in the anterior cingulate and rolandic operculum that were not identified for any of these three individuals.

Table 6. Comparison of PET study results for significantly activated neural regions

Lobe	Region (BA)	Subject 1		Subject 2		Subject 3		Brown et al. (2005)	
		L	R	L	R	L	R	L	R
Frontal	Supplementary motor area (6)	X	X	X	X	X	M	X	
	Precentral gyrus (4)	X	X	X	X	X	X	X	X
	Premotor cortex (6)	R	X	X	X	X	X		X
	Prefrontal (10)	M	M	M	M	X		X	
	Frontal operculum (45)	X		R	M				X
	Cingulate motor area (24)	X	M	X				X	
	Inferior frontal gyrus (47)	M		R	X	M			X
	Superior frontal gyrus (8)			R	M				X
Limbic	Anterior cingulate (24)	M	M		R	X		X	X
Parietal	Inferior parietal lobe (40)	R	R	X	R	X	M	X	X
	Rolandic operculum (43/4)			R		R		X	X
Temporal	Superior temporal gyrus (22)	R	X	X	R	X	X	X	
	Middle temporal gyrus (21)	X		X	X	M		N	N
Sub-lobar	Anterior insula (13)	X		X	R	R	R		X
	Putamen	R	X						
	Globus Pallidus	M	M	R					
	Caudate	X	X	M	M				
Cerebellum	Lobule VI	X	X	X	X	X	R	X	X
	Vermis III/IV	X	R	X	X	R	X		X
	Vermis VI	X	R	X	R	X	X		X

Subject 1 is male, Subjects 2 & 3 are female. The Brown et al. (2005) meta-analysis included eight studies involving either male or female persistent stutterers who engaged in various vocal tasks, including oral reading (minus rest) and monologue (minus rest) conditions. X indicates regional activation, N indicates no reported data for the region. An X marked below Brown et al.'s (2005) paper indicates regional activation in at least one instance across the eight studies. R denotes regions activated only during oral reading (minus rest) tasks; M denotes regions activated only during monologue (minus rest) tasks.

CHAPTER 4: DISCUSSION

Summary of Findings

This investigation was designed to explore the patterns of neural activity in individuals who stutter and to compare these patterns with previously published neural activation data from groups of stutterers. Overall, no distinct pattern of activity was demonstrated by the three stuttering individuals included in this study. Significant activations and deactivations were idiosyncratic; no specific hemisphere or region emerged as being noteworthy in all speakers. Correlations of all three subjects' activity averaged together showed a moderate relationship between the two speech tasks as well as between the two hemispheres during both activations and deactivations, though this finding was not supported in correlations of the three subjects' activity individually. The lack of consistency, and the differences between individual and group data, stand in contrast to previously published data from groups of stutterers (Brown et al., 2005). The following sections will review this apparent discrepancy in greater detail.

Individual Activity

As previously mentioned, the overall question regarding the three individuals was whether any specific patterns of neural activity would be demonstrated during the two speaking conditions of oral reading and monologue. The data from the participants showed that, while some significant activations and deactivations were observed throughout the observed regions in any given individual, the patterns of activity were

idiosyncratic and did not follow any distinct pattern. In fact, the three individuals were more discrepant in their neural activity than alike.

The apparent lack of any pattern in stuttering individuals seemingly contradicts the findings and proposed neural markers of stuttering presented by Brown et al. (2005). The first proposition by Brown and colleagues, that stutterers show overactivity in the right frontal operculum and anterior insula, is not replicated here. While some activation in these areas is seen in the participants of this study, the activity is minimal and provides less than convincing evidence for a trend similar to that seen in the meta-analysis. The second proposed marker, that auditory areas are less active in stutterers, is challenged by present results showing significant activity bilaterally in the STG and at least unilaterally in the MTG of all three participants. The activity seen here is unique, as Brown et al.'s (2005) meta-analysis and other previously published data has shown reductions and even an absence of auditory activations (Braun et al., 1997; Fox et al., 1996; Stager et al., 2003; Van Borsel et al., 2003) as well as negative correlations between stuttering rate and auditory activity in men (Fox et al., 2000; Neumann et al., 2003) and women (Ingham et al., 2004). Cerebellar activity in the vermal portion of lobule III, the third of the proposed neural markers, is the only one of the three that is upheld by the current results; specifically, bilateral activations were demonstrated in at least one of the task conditions by all three participants.

Correlational data of the group average of the three subjects suggest a moderate relationship between oral reading and monologue activity in both hemispheres as well as between left and right hemispheric activity during both speech tasks. Furthermore, group correlations do not indicate a relationship between activations and deactivations in either

hemisphere during either speech task. These relationships are not consistently demonstrated in each individual, however; in fact, the correlations for each category varied considerably for each subject.

The discrepancies between individual data reported here and previously published group results are an unexpected finding. Ordinarily, individuals who comprise a specific group of people would demonstrate patterns of behavior similar to that of the group as a whole, not just in terms of brain activity during stuttering but in human behaviors in general. This similarity is not only absent in the comparisons of this study, but the individuals occasionally demonstrated completely opposite behavior from the group to which they were compared.

This difference could be due, in part, to modifications in the quality of measurement techniques. Numerous improvements have been made to imaging technology over the past five to ten years in order to achieve greater accuracy and specificity of results. The data from this study are the result of such improvements; specifically, the PET system used to collect the individual data for this study is a state-of-the-art piece of equipment that enabled precise measurements unlike those performed in previous group studies. For example, this system is able to acquire images in 3D mode, increasing sensitivity fourfold (see Appendix A for further details regarding this PET system). With such major improvements in imaging techniques, it is plausible that the individual patterns of neural activity demonstrated in this study were able to be identified because of improved technology rather than a true discrepancy from previous group patterns.

In fact, this advanced technology is being used in additional research currently being performed by the research group at the Research Imaging Center of the University of Texas Health Science Center at San Antonio headed by Drs. Fox, Ingham, and colleagues. Interestingly, these researchers have also found individual stutterers to demonstrate neural activity incongruous with groups of stutterers. (Ingham, personal communication, 6/24/2008). Performing both group and individual research simultaneously, Ingham and colleagues are taking individual stutterers from a larger group study and conducting comparative investigations similar to that of this current study. Preliminary data from this research has shown distinct neural activity in the individuals that does not compare to previous group data, replicating the results of this current study. This is additional evidence to suggest that current imaging technology is providing more accurate information regarding the brain activity of stutterers. Thus, it is quite possible that groups of stutterers might demonstrate neural activity similar to the individuals described in this study were they to be studied using similar technology. Future studies of groups of stutterers will hopefully utilize improved technologies to investigate the disorder, which will then lead to more fruitful comparisons with stuttering individuals.

Another possibility, however, is that technology may not play such an influential role in study results. An earlier PET study by Fox Ingham, and colleagues (Fox et al., 1996) reported neural activity in terms of group data as well as the level of consistency with this group data demonstrated by each individual. Using ten dextral males (ages 21-36, mean age 32), Fox and colleagues first calculated the neural activations and deactivations present during oral reading for the males as a group, and then determined

the extent to which each individual's regional activations matched the group as whole, also referred to as penetrance data. Penetrance values ranged from 60-100%, indicating that while some subjects perfectly matched the group in patterns of activations, others only demonstrated similar activity in 60% of brain activations (Fox et al., 1996). In this case, the lack of similarity can not be attributed to differing technology, as the individuals used in comparison to the group came from the same study and were imaged using the same type of technology. So, while some evidence suggests that newer technology is allowing for increased accuracy and specificity of results in imaging studies of stuttering that could potentially explain the inconsistencies in individual versus group data, other evidence counters that claim.

The use of differing analysis methods is another potentially confounding factor in the comparison of individual and group data. Until the late 1990s, the method of choice when analyzing brain data of stutterers was to use within-subject conditional contrasts (see Introduction, p. 20-21, for detailed description), which has since been determined to be a sub-par experimental strategy primarily because this method assumes that a behavior of interest can be isolated to one condition, which is not entirely possible to do with the behavior of stuttering. An alternative approach, known as performance correlation analysis, relies less on the strength of focal responses in regional brain activity and instead operates upon the theory that the amount of brain activity demonstrated during an imaged task is highly correlated to the rate at which a behavior (e.g., stuttering) occurs. Hence, the more that stuttering occurs, the more neural activity that can be seen and analyzed. As conditional contrasts were used to analyze the individual data for this study, it is entirely possible that the activations and deactivations demonstrated by each

individual are not an accurate portrayal of the neural activity associated with their stuttering. It would be of benefit to utilize performance correlation analyses for the individual data of this study to achieve a more truthful picture of their brain activity. Furthermore, the group data to which individual data was compared included both types of analyses; out of eight studies included in the Brown et al. (2005) meta-analysis, three used performance correlations and five used conditional contrasts. Comparison between individual and group data would be further bolstered if the method of analyses was consistent for both groups.

Considering the variables mentioned above that may be partially responsible for the discrepancies seen between individual and group data shown in this study, the greatest assertion that can be made from the results presented here is that further research is necessary on all fronts in order to better understand the disorder of stuttering. Future research using performance correlation analyses will provide more accurate information regarding the brain activity of individuals as well as groups of individuals who stutter. Additionally, the new technology available today can achieve unparalleled precision when gathering imaging data. While there are limiting factors regarding the use of this technology, such as cost and availability, researchers performing both types of studies should aim to use this in an effort to produce the most reliable data regarding brain activity of stutterers.

Hopefully, future research endeavors along these lines will shed more light upon the possibility that stuttering individuals do no demonstrate neural activity similar to that of groups of stutterers, as suggested by the three individuals in this study. This is imperative for several reasons. First and foremost, if group data are not truly

representative of the stuttering population, it is misleading if they are reported as such, as this can have a detrimental effect on research about this disorder. For instance, when group studies result in such robust findings, such as the body of literature suggesting reduced activity in auditory areas of stutterers, researchers are led to pursue certain paths of study with the assumption that this pursuit will deepen our understanding of stuttering. This line of research, however, may ultimately prove to be of little value to stuttering research and treatment when, for instance, it is discovered that the patterns revealed in the group data are accidental and unrelated to the neural activity of individual stutterers. And as shown in this current study, these three individual stutterers did not demonstrate neural activity patterns that matched patterns demonstrated in previous group research. Several factors discussed above could have contributed to this difference, therefore replication of this finding is essential.

Secondarily, if the disparity between neural activity of individuals and groups is authenticated, the use of group studies has questionable clinical ramifications as well. With a growing push towards evidence-based practice in the field of clinical speech language pathology, clinicians are now more than ever turning to research studies in order to learn the most effective therapy targets and techniques. It is quite possible that practicing speech language pathologists could interpret the results of group imaging studies of stutterers that have been published over the last decade, and most notably the results published by Brown and colleagues (2005), to mean that all stutterers display certain neural activity patterns. Consequently, therapy goals created with this research in mind could, in fact, be futile. It is imperative that further research be undertaken to

corroborate or refute the suggestion of four neural markers of stuttering proposed by Brown et al. (2005).

Lastly, there is a great need for continued investigations of whether behavioral treatments bring about changes in areas thought to demonstrate atypical activity. While it is necessary and crucial for research to determine the neural patterns of stutterers, it is paramount that this knowledge leads to successful treatment protocol. This step that will ultimately prove the worth of imaging studies of stuttering.

Task-dependent Activity

Another initial question asked whether the specific tasks of reading and monologue would result in any activity that occurred only in that particular condition. Activity in each condition was indiscriminate, with no overt pattern emerging for task-dependent activity. The prefrontal cortex, however, was distinct in that two of the three participants demonstrated activations during the monologue task and all three showed deactivations while reading. Even taking this activity into account, these results do not offer convincing evidence of neural activity that is specifically linked to reading or monologue tasks. More individual data, however, may lead to a different conclusion as well as provide a clearer overall picture of patterns of activity during reading and monologue tasks.

Gender-specific Activity

A third question posed in this study was whether any gender differences would be seen in the individual data. The gender differences in regional control of stuttering proposed by Ingham et al. (2004), however, are not supported in the present results.

Whereas Ingham et al. (2004) demonstrated state effects for each gender, specifically in the frontal lobe and cerebellum in males and the basal ganglia in females, present results demonstrate no such effects. The two females in this study showed an overall lack of significant activations in the putamen, while the male demonstrated bilateral activations. The male also showed bilateral activations in the globus palidus during the monologue task, though only one of the females showed activation in the globus palidus in only one of the two tasks. Both genders showed only left activations in the caudate during each task.

General Conclusions and Implications

While results of this study have shown surprising differences between individual and group brain activity data during stuttering as well as raised interesting questions regarding the utility of group studies of stuttering, further investigation is necessary on many levels to bolster current findings. The primary limitation of this study is the small number of participants; three participants do not provide enough insight and data to tease apart the potential differences in neural activity of individual stutterers versus groups of stutterers. Future studies should investigate a larger sample of individual subjects. Additionally, the performance correlation methods should be used, in conjunction with the newest imaging technology, if possible, in order to gain more accurate data and better understand the intricacies of individual stutterers' neural activity.

The primary results of this study, in summary, include the following. First, these three individual stutterers show an indiscriminate pattern of activity in regions related to speech and hearing. Second, data from these three individual stutterers intermittently

corresponds with data from studies of groups of stutterers; they do not demonstrate the overactivations of the right frontal operculum and anterior insula that are seen groups of stutterers, nor do they demonstrate reduced or absent activity in auditory areas similar to that of group studies of stutterers. These three individual stutterers do resemble group data in the activation patterns seen in the vermis of lobule III in the cerebellum, though. Third, the individual data from the three participants in this study do not suggest any neural activity that is specific to a certain task (i.e., activations during only reading tasks or only monologue tasks). Fourth, no overt activity pattern specific to either gender emerged in the present results.

In addition to these main results, the methodological implications of these outcomes suggest that the use of more current imaging technology and different analysis methods may provide a much clearer picture of the neural activity of both stuttering individual and groups of stutterers. And here it is appropriate to reiterate the primary reason that stuttering research has turned to imaging technology as a means of investigation, as stated by Fox in his 2003 discussion of brain imaging and stuttering:

> "Ultimately, what is needed are explanations at the neural system level as to how speech production is organized and executed, how the speech system is dysregulated so as to produce the execution errors collectively termed stuttering, *and how fluency inductions and treatments achieve behavioral normalization*" (pp. 268, emphasis added).

The ultimate end of this line of research will be, hopefully, treatments that can produce improved fluency for people who stutter. This study calls into question the present course of investigation, that of studying groups of stutterers, as it appears that the

individual stutterers whom we aim to rehabilitate may not demonstrate neural patterns that match those of groups of stutterers. Several methodological variables could be responsible for this difference, however, and therefore should be investigated further. In sum, future research utilizing newer technology and improved analysis methods is required to further understand the brain activity involved in stuttering, both in individuals as well as groups, as well as to clarify whether or not individuals to indeed demonstrate neural activity unlike groups of stutterers. These investigations will hopefully provide unique and clarifying data that can offer researchers a better understanding of the neural regions involved in stuttering, which in turn can lead to the development of effective stuttering treatments.

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APPENDIX A

DETAILED DESCRIPTION OF ORIGINAL DATA AND IMAGE ACQUISITION FROM INGHAM (2006)

Neurophysiologic Imaging (PET)

Functional imaging was performed using $H^2{}_{15}O$ PET. Subjects in each group were imaged serially. Each subject completed 5 PET imaging sessions at intervals of weeks to months. All PET imaging were performed on a research-dedicated Siemens/CTI HR+. This state-of-the-art PET system (installed 2002) acquires 63 simultaneous axial (horizontal) planes over a transaxial field of view of 15.5 cm, sufficient to cover the entire brain. The in-plane resolution is 4.1 mm FWHM (full-width at half maximum), equal to or better than that used in the majority of fMRI studies. For this project, all PET images were acquired in 3D mode, which increased sensitivity by a factor of ~4 and lowered the radiation dose required per scan to ~20 mCi. Over the entire series of scanning sessions, the total administered dose was 480 mCi (20 mCi x 6 scans x 5 sessions); this was well within the FDA guidelines for a single scanning session.

Imaging Conditions

Each session consisted of 6 scans, two during each of 3 conditions: eyes closed rest (Rest), oral paragraph reading (Read), and monologue (Speak). The Read condition employed paragraphs used in Fox et al. (40) that were visually presented on an LCD flat-panel monitor adjustable for a comfortable reading distance (~ 14 inches). The Monologue condition used the Iowa Job Task (83). During both speaking conditions, subjects were recorded (audiovisually) using a digital video camera mounted below the

LCD screen. Scan task digital recordings were scored by blinded observers for %SS scores and nonstuttered syllables per scanning epoch using SMS (Ingham et al., 1999). These scores will be used for performance correlation analyses. Parallel recordings of oral reading and monologues were collected within the TEST protocol and were used to verify the relationship between speech performance during scanning and non-scanning conditions.

Image Registration and Normalization

Image processing employed published methods and a combination of in-house, commercial and public-domain software. For each subject, PET images were corrected for motion within session and co-registered across sessions using Woods' algorithm (Woods, Cherry, & Mazziotta, 1992; Woods, Mazziotta, & Cherry, 1993). PET images had scalp and skull removed by a threshold-based shrink-wrap procedure. For each subject, the scalped PET image was co-registered to the scalped high-resolution T1-MRI image using the Convex Hull algorithm (Lancaster, Fox, Downs, Nickerson, Hander, El Mallah et al., 1999). As the T1-MRI images was already been placed in standard space relative to the Talairach atlas (Talairach & Tournoux, 1988), MRI co-registration placed PET data into the same space.

APPENDIX B

RAW ACTIVATION & DEACTIVATION DATA FOR ALL THREE SUBJECTS

SUBJECT ONE

Regions of Interest		ACTIVATIONS				DEACTIVATIONS			
		LH-OR	LH-MON	RH-OR	RH-MON	LH-OR	LH-MON	RH-OR	RH-MON
FRONTAL	SMA (6)	24	213	0	168	91	0	41	35
	Pre-central gyrus (4)	277	484	125	0	116	52	135	80
	SLPrM (6)	161	363	18	49	85	61	0	138
	Prefrontal (10)	0	168	16	74	168	52	169	212
	Cingulate motor area (24)	42	53	0	198	110	36	0	256
	Frontal operculum (45)	28	146	0	85	0	34	0	29
	Inferior frontal gyrus (47)	0	34	45	0	0	0	0	16
	Superior frontal gyrus (8)	0	0	0	0	42	307	54	466
LIMBIC	Anterior cingulate	0	43	33	0	91	0	69	159
PARIETAL	Inferior parietal lobe (40)	53	0	0	0	39	96	109	77
	Rolandic operculum (43/4)	0	0	0	41	0	31	35	0
TEMPORAL	STG (22)	24	0	0	79	0	142	158	54
	MTG (21)	54	32	0	19	0	21	19	75
SUB-LOBAR	Caudate	20	218	61	86	0	0	38	0
	Globus Palidus	0	48	203	63	370	0	0	38
	Putamen	36	0	0	0	0	0	0	0
	Anterior insula (13)	102	241	0	0	29	0	97	23
CEREBELLUM	Lobule VI	412	635	233	410	0	81	0	119
	Vermis III/IV	140	262	49	0	0	44	21	101
	Vermis VI	100	86	20	0	36	81	218	63

SUBJECT 2

Regions of Interest		ACTIVATIONS				DEACTIVATIONS			
		LH-OR	LH-MON	RH-OR	RH-MON	LH-OR	LH-MON	RH-OR	RH-MON
FRONTAL	SMA (6)	103	168	233	133	26	259	137	146
	Pre-central gyrus (4)	176	315	240	46	122	57	291	505
	SLPrM (6)	176	57	240	23	0	0	214	113
	Prefrontal (10)	0	177	0	192	165	0	226	0
	Cingulate motor area (24)	86	21	0	0	136	281	53	0
	Frontal operculum (45)	140	0	0	17	0	0	0	0
	Inferior frontal gyrus (47)	152	0	95	65	17	168	19	112
	Superior frontal gyrus (8)	24	0	0	42	16	15	48	117
LIMBIC	Anterior cingulate	0	0	82	0	143	102	42	33
PARIETAL	Inferior parietal lobe (40)	111	64	44	0	235	283	361	608
	Rolandic operculum (43/4)	22	29	0	0	0	0	0	0
TEMPORAL	STG (22)	51	193	26	0	0	0	118	79
	MTG (21)	165	362	174	157	20	0	0	59
SUB-LOBAR	Caudate	0	55	0	59	0	0	0	58
	Globus Palidus	16	0	0	0	0	0	0	0
	Putamen	0	0	0	0	35	15	0	24
	Anterior insula (13)	38	25	62	0	0	0	0	58
CEREBELLUM	Lobule VI	184	148	187	192	88	39	0	0
	Vermis III/IV	39	54	73	52	63	82	22	0
	Vermis VI	29	24	152	0	0	0	0	0

SUBJECT 3

Regions of Interest		ACTIVATIONS				DEACTIVATIONS			
		LH-OR	LH-MON	RH-OR	RH-MON	LH-OR	LH-MON	RH-OR	RH-MON
FRONTAL	SMA (6)	149	167	0	32	153	68	152	80
	Pre-central gyrus (4)	421	172	207	340	331	149	516	182
	SLPrM (6)	315	156	172	227	0	53	0	19
	Prefrontal (10)	37	15	0	0	153	0	17	0
	Cingulate motor area (24)	0	0	0	0	35	0	15	0
	Frontal operculum (45)	0	0	0	0	0	0	0	0
	Inferior frontal gyrus (47)	0	22	0	0	0	0	108	0
	Superior frontal gyrus (8)	0	0	0	0	83	0	17	0
LIMBIC	Anterior cingulate	16	27	0	0	0	0	81	0
PARIETAL	Inferior parietal lobe (40)	18	19	0	54	163	44	357	168
	Rolandic operculum (43/4)	17	20	0	0	0	0	0	0
TEMPORAL	STG (22)	180	77	116	204	0	0	0	0
	MTG (21)	0	28	0	0	0	22	361	0
SUB-LOBAR	Caudate	0	0	0	0	61	34	44	31
	Globus Palidus	0	0	0	0	0	0	32	20
	Putamen	48	0	0	0	42	0	119	18
	Anterior insula (13)	23	0	88	0	0	0	19	0
CEREBELLUM	Lobule VI	209	130	266	72	0	96	34	34
	Vermis III/IV	39	0	23	67	95	0	66	74
	Vermis VI	160	42	78	199	18	0	0	0

APPENDIX C

POSITIVE & NEGATIVE CORRELATIONS FOR EACH SUBJECT AND ALL THREE SUBJECTS COMBINED

SUBJECT 1	ACT-LH-OR	ACT-RH-OR	ACT-LH-MON	ACT-RH-MON	DEACT-LH-OR	DEACT-RH-OR	DEACT-LH-MON	DEACT-RH-MON
ACT-LH-OR	1.00	0.16	0.59	-0.03	-0.14	-0.05	0.32	0.17
ACT-RH-OR		1.00	0.58	0.01	0.14	-0.11	-0.08	0.11
ACT-LH-MON			1.00	0.27	0.18	-0.07	-0.04	0.18
ACT-RH-MON				1.00	0.01	-0.32	0.00	0.02
DEACT-LH-OR					1.00	0.26	0.04	0.54
DEACT-RH-OR						1.00	0.36	0.16
DEACT-LH-MON							1.00	0.58
DEACT-RH-MON								1.00

SUBJECT 2	ACT-LH-OR	ACT-RH-OR	ACT-LH-MON	ACT-RH-MON	DEACT-LH-OR	DEACT-RH-OR	DEACT-LH-MON	DEACT-RH-MON
ACT-LH-OR	1.00	0.68	0.41	0.35	0.07	0.23	0.24	0.35
ACT-RH-OR		1.00	0.47	0.35	0.13	0.26	0.23	0.43
ACT-LH-MON			1.00	0.46	0.21	0.40	-0.09	0.32
ACT-RH-MON				1.00	0.24	0.11	0.05	0.11
DEACT-LH-OR					1.00	0.54	0.73	0.11
DEACT-RH-OR						1.00	0.47	0.57
DEACT-LH-MON							1.00	0.33
DEACT-RH-MON								1.00

SUBJECT 3	ACT-LH-OR	ACT-RH-OR	ACT-LH-MON	ACT-RH-MON	DEACT-LH-OR	DEACT-RH-OR	DEACT-LH-MON	DEACT-RH-MON
ACT-LH-OR	1.00	0.79	0.66	0.84	0.21	-0.01	0.44	0.43
ACT-RH-OR		1.00	0.50	0.80	-0.11	-0.17	0.37	0.26
ACT-LH-MON			1.00	0.69	-0.03	0.16	0.62	0.24
ACT-RH-MON				1.00	0.22	-0.01	0.54	0.52
DEACT-LH-OR					1.00	0.42	0.30	0.54
DEACT-RH-OR						1.00	0.47	0.55
DEACT-LH-MON							1.00	0.73
DEACT-RH-MON								1.00

ALL SUBJECTS	ACT-LH-OR	ACT-RH-OR	ACT-LH-MON	ACT-RH-MON	DEACT-LH-OR	DEACT-RH-OR	DEACT-LH-MON	DEACT-RH-MON
ACT-LH-OR	1.00	0.57	0.53	0.42	0.04	0.02	0.35	0.30
ACT-RH-OR		1.00	0.50	0.40	0.05	-0.02	0.22	0.28
ACT-LH-MON			1.00	0.47	0.15	0.13	0.16	0.35
ACT-RH-MON				1.00	0.14	-0.08	0.21	0.23
DEACT-LH-OR					1.00	0.41	0.35	0.39
DEACT-RH-OR						1.00	0.38	0.40
DEACT-LH-MON							1.00	0.53
DEACT-RH-MON								1.00