NEUROANATOMICAL DIFFERENCES IN ADULTS AND CHILDREN WHO STUTTER: A VOXEL-BASED MORPHOMETRY STUDY

BY

HATUN ZENGIN

THESIS

Submitted in partial fulfillment of the requirements
for the degree of Master of Arts in Speech and Hearing Science
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2011

Urbana, Illinois

Master's Committee:

Assistant Professor Torrey M. J. Loucks, Chair
Associate Professor Nicoline Ambrose
Assistant Professor Christopher M. Grindrod

ABSTRACT

Background: Previous functional and anatomical neuroimaging studies have reported physiological and structural differences in adults who stutter and children who stutter compared to fluent controls. However, a comparison of neuroanatomical differences between adult group and children group has not been reported in the literature. The current study examined neuroanatomical differences in groups of adults and groups of children separately. This study reported on the neuroanatomical changes in brains of people who stutter from childhood to adulthood by descriptively comparing the results of the adult data and child data. Using the same dataset, the present study also attempted to replicate the comparisons in Chang et al. (2008) study. **Methods:** High resolution MRI data from adult and children groups were analyzed separately with voxel-based morphometry (VBM), an unbiased, whole-brain based volumetric technique. Adult group comparisons consisted of adults who stutter (*n*=12) versus adult controls (*n*=25), and pediatric group comparisons included recovered children (*n*=7); children with persistent stuttering (*n*=8), and normally fluent children (*n*=7). **Results:** Our findings demonstrated significant gray and white matter volume differences in brain areas important for speech production in adults who stutter, children with persistent stuttering, and recovered children relative to controls. These areas included subcortical structures, cortical areas, as well as cerebellar regions. **Conclusions:** Developmental stuttering could be related to aberrant gray and white matter volumes in a widely distributed neural network which may lead to disrupted transmission of sensory or motor information among speech relevant areas in this neural circuitry. In addition, aberrant development pattern in these areas may present risk for the onset of stuttering.

ACKNOWLEDGMENTS

I am thankful and appreciative to all the people who have supported me as I completed my master's thesis. I would like to thank my advisor, Dr. Torrey Loucks, for his time, guidance, and understanding to help further my research and writing skills throughout this project. I also owe many thanks to my committee members, Dr. Nicoline Ambrose and Dr. Christopher Grindrod, who generously offered their time, expertise, and encouragement throughout the entire process.

I am grateful for the MRI data from the longitudinal studies of the Illinois Stuttering Research Project, and I would like thank the participants in this study, for their willingness to contribute to increase our understanding of the mechanisms underlying stuttering.

Thanks also to my friends and peers who supported me and encouraged me in this process. Thanks to my fellow research assistant, Ai Leen Choo, for helping me stay motivated and for offering me her insights.

Finally, I would like to thank my husband, Erdem Bolatkale, my parents Nazif and Fatma Zengin, and my entire family for their unwavering support, encouragement, and love as I accomplish my goals.

Table of Contents

CHAPTER I: INTRODUCTION

Stuttering is a developmental speech production disorder whose etiology still remains unknown. Stuttering has an onset in early years of childhood, and has a hereditary component. The symptoms and epidemiology of stuttering are well-documented in the literature. However, investigations of the biological mechanisms underlying this disorder are relatively new. Recently, there have been several reports of specific chromosomes that are associated with liability to developmental stuttering. In addition, there have been efforts to investigate neurophysiological and neuroanatomical basis to stuttering. The functional neuroimaging studies of stuttering have reported atypical activation patterns in several regions of the brain involved in speech control in people who stutter. Following up on the evidence from functional studies, researchers have studied neuroanatomical basis to stuttering and they identified significant structural differences between people who stutter and fluent speakers. Of these structural neuroimaging studies, only Chang, Erickson, Ambrose, Hasegawa-Johnson & Ludlow (2008) reported on the neuroanatomical differences in the brains of a pediatric sample as opposed to an adult sample. A comparison of neuroanatomical differences between adult group and children group has not been reported in past research. Therefore, in this study, we will conduct pair-wise comparisons of adults who stutter versus adult controls, children who stutter versus fluent controls, and persistent versus recovered children. We will then descriptively compare the patterns of results in our child data and adult data. This study will also attempt to replicate the comparisons in Chang et al. (2008) study.

CHAPTER II: LITERATURE REVIEW

Definition and characteristics of stuttering

Stuttering is a developmental speech production disorder, which can negatively impact several domains of a person's life, including communicative, psychological, sociological and emotional well being. It has long been recognized that an agreeable definition of stuttering does not exist (Bloodstein & Ratner, 2008; Manning, 2009; Packman & Attanasio, 2004; Yairi & Ambrose, 2005). The World Health Organization (WHO) defines stuttering as "disorders in the rhythm of speech in which the person knows precisely what he wishes to say, but at the time is unable to say it because of an involuntary, repetitive prolongation or cessation of a sound" (as cited in Manning, 2009). According to Wingate's (1964) operational definition, stuttering is "(a) Disruption in the fluency of verbal expression, which (b) characterized by involuntary, audible, or silent repetitions or prolongations in the utterance of short speech elements, namely: sounds, syllables, and words of one syllable. These disruptions (c) usually occur frequently or are marked in character and (d) are not readily controllable." (as cited in Bloodstein & Ratner, 2008).

Bloodstein & Ratner (2008) pointed out that conventional definitions of stuttering fall short when it comes to identifying the causal factors, as well as objectively differentiating stuttering from other forms of disfluency. The fact that all speakers experience disfluency in their speech calls for an objective and comprehensive definition of stuttering that differentiates the disorder of stuttering from disfluency. A more comprehensive definition of stuttering, would describe the types, frequency, length or repetition, and physical characteristics of disfluencies and stuttering, but to be a true definition of a disorder, it must extend beyond describing the disorder to include causal mechanisms, whether stuttering is a neurological, linguistic,

psychological or a psychiatric disorder. Causal mechanisms however remain undetermined. The purpose of the current project is to test for neurological differences associated with the presence of stuttering that could explain a range of factors related to causation, development, persistence, and recovery.

Symptoms of Stuttering

It is important to discuss the symptoms of stuttering because part of understanding stuttering involves determining whether the symptomatology differs from typical disfluencies that would support the inference that different mechanisms underlie different disfluencies. Yairi and Ambrose (2005) suggest two global disfluency classes: Stuttering-Like Disfluencies (SLD) and Other Disfluencies (OD). SLD's include part-word repetitions, single-syllable word repetitions, and disrhythmic phonation while OD's consist of interjections, multiple-syllable word and phrase repetitions, and revision or abandoned utterance. Yairi and Ambrose suggest SLD's are *statistically* most common, but not exclusive, in the speech of people who stutter (2005). Yairi and Ambrose (2005) consider the frequency distribution of the types of disfluencies is a central factor in differentiating stuttering as a disorder and qualitatively distinguishing disfluency types.

In their large scale normative disfluency study, Yairi and Ambrose found statistically significant differences between children who stutter and control group in stuttering-like disfluencies (part-word repetitions, single-syllable word repetitions, disrhythmic phonations). The results indicated that children who stutter had a mean frequency of 11.30 total SLD per 100 syllables (SD= 6.64) while children in the control group had a mean of 1.41 (SD= .96). Yairi and Ambrose (2005) reported that the mean frequency of other disfluencies (OD) were more similar

for both groups (5.79 for children who stutter and 4.48 for control group). In the same normative study, Yairi and Ambrose (2005) found that besides types and frequency of disfluencies, the mean number of repetition units per instance also discriminate between children who stutter and control group (3.12 multiple unit repetitions per 100 syllables for stuttering group and 0.19 for control group. This information is also important in differentiating stuttering from normal disfluencies.

A second differentiation is that SLD are can be accompanied by a number of physical behaviors as well as psychological concomitants are observed to accompany stuttering behavior in children and adults. Eyeblinks, wrinkling of the forehead, frowning, visible tension in the face, and jerking of the head are listed as some of the most common behaviors (Bloodstein & Ratner, 2008), but other concomitants such as vocal abnormalities, sharp shifts in pitch and loudness level, perspiration, respiratory difficulties, increase in the heart and pulse rate are documented. Mulligan, Anderson, Jones, Williams & Donaldson (2001) found that adults who stutter had more involuntary movements accompanying disfluencies than those in the control group (24.4% vs. 4.5%). Disfluencies and physical concomitants can further be accompanied by negative patterns of attitudes in order to cope with stuttering such as finding speech unpleasant and threatening, feeling embarrassed and trying to avoid speaking, low self-esteem and poor self-concept (Bloodstein & Ratner, 2008). These accompanying behaviors are not seen in disfluencies of normally fluent speakers, therefore they differentiate stuttering from other disfluencies. Whether these behaviors are secondary to this disorder or characteristics related to neurological or genetic causes remains unknown.

Epidemiology of Stuttering

The distribution of stuttering in the population suggests this disorder has specific characteristics that are consistent with biological causation. Craig, Hancock, Tran, Craig & Peters (2002) conducted a telephone interview study with 12,131 participants in order to investigate the prevalence and incidence of stuttering. Craig et al. (2002) estimated the prevalence of stuttering for the whole population is .72 cases per 100 people with at least a 50% higher prevalence rate of stuttering in males. They found stuttering is more prevalent among young children (1.44 cases per 100 children) than adults with younger children having a higher prevalence of stuttering among male children compared to female children (2.3- 3.3:1). The stuttering prevalence was .53% in adolescents with (4:1 male-to-female ratio) and .37 % for older adults over the age of 51 (1.4:1 ratio). Their results clearly indicated that stuttering is most prevalent among young children and that males have greater risk of stuttering. In line with Mansson's finding, Bloodstein and Ratner (2008)'s review of six epidemiology studies showed that approximately 5% of the population has ever stuttered in life. Along with the incidence and prevalence rates reported in the literature, using similar longitudinal methods, Yairi and Ambrose (2005; Ambrose and Yairi, 1999) also showed that there was 74% recovery and 26% persistence rate in children even when measured conservatively.

Strong empirical evidence for this general distribution was reported in a longitudinal study by Mansson (2000) studied the incidence of stuttering in the island of Bornholm (Denmark) in all children born in the island in 1990 and 1991 before they turned 3 years old. Of the 1,021 children who participated, 53 were identified as stuttering. In the surveys conducted at age 3, 5 and age 9, the total incidence over 9 year period was estimated to be 5.19%. Among the 53 children who stuttered, the male-to-female ratio was 1.65:1. Two years after the first

screening (at age 5), Mansson re-evaluated the 53 children who stutter and identified only 15 of them as still stuttering. Based on this finding, he concluded that the recovery rate of stuttering was 71.4%, while the persistency rate was 28.4%. As Bloodstein & Ratner (2008) pointed out, the fact that more than 70% of the cases recovered by age five would lower the prevalence rate among school-aged children. This study showed that distribution of stuttering is highly specific. The study also indicated that stuttering is a developmental disorder which is most common in males. This distribution was significantly lower by age five.

Onset of Stuttering

The pattern of stuttering is important to consider because it provides some clues as to whether stuttering is a learned behavior or a developmental disorder. Under a learning perspective, stuttering should have a gradual onset, but the evidence is contrary to this presumption because stuttering can have a sudden onset in the early years of life. It is clear that stuttering is not accompanied by apparent brain damage or co-occurring pathology but neither are necessary attributes of stuttering. What is more likely is that the current metrics for neurological or biological involvement are not sensitive to developmental speech disorders.

The early and frequently rapid onset argues against simple predisposing factors. Based on 163 children, the mean age of stuttering onset 33 months ranging from 20 to 48 months with more than 85% beginning before 42 months and 59% occurring during the third year of life (Yairi and Ambrose, 2005). There seems to be a greater risk of onset in the lower half of the sample age range. In the same study, Yairi and Ambrose (2005) reported relatively few new onsets occurred after the age of 3 or 4, which agrees with Mansson's (2000) findings.

Stuttering: A developmental disorder with a genetic basis

Given the evidence that developmental stuttering emerges at a young age without accompanying brain damage, emotional disorder, speech/language disorder or any other known cause, but remains specific to development and a higher male susceptibility, many thinkers have posited a genetic basis. Several research groups have provided accumulating evidence that persistent developmental stuttering (PDS) has a hereditary component (Andrews, Morris-Yates, Howie & Martin, 1991; Dworzynski , Remington, Rijsdijk, Howell & Plomin, 2007; Felsenfeld, Kirk, Zhu, Statham, Neale & Martin, 2000; Riaz et al., 2005; Shugart et al., 2004; Suresh et al., 2006; Viswanath, Hee & Chakraborty, 2004; Wittke-Thompson et al., 2007).

In order to identify the relative importance of environmental and genetic influences on stuttering, researchers conducted twin studies. Andrews et al. (1991) and Felsenfeld et al. (2000) conducted twin studies, comparing fraternal and identical twins, in order to investigate hereditary components of PDS. Among 50 monozygotic same-sex, and 37 dizygotic same-sex nonclinicial pairs with PDS Andrews et al. (1991) identified that 20% of the monozygotic pairs (10 pairs; 4 female and 6 male) were concordant compared with 2 pairs (1 male and 1 female) in the dizygotic pairs (5.4%). Out of the 48 dizygotic opposite-sex pairs, only one pair was concordant. Andrews et al. tested behavioral models attributing the variance in expression of stuttering to shared environmental factors, genetic variance, unique or non-shared environmental factors. Their model attributing 71% of the variance in susceptibility to stuttering to additive genetic variance with the remaining 29% attributed to individual's unique environmental factors. In a larger study, Felsenfeld et al. (2000) screened 1567 twins and 634 individuals using questionnaires and phone interviews. They identified 17 monozygotic and eight dizygotic pairs who were concordant for stuttering. Statistical analyses identified that additive genetic effects

accounted for approximately 70% of the variance and the remaining 30% were attributed to the individual's unique environment, which are highly similar to the findings of Andrews et al. (1991).

Family-based studies were also used to disentangle the issue of stuttering as a disorder caused by hereditary versus environmental factors. These studies have been used to identify the degree of risk of relatives developing stuttering when a member of the family is a person who stutters. Ambrose, Yairi and Cox (1993) studied the incidence of stuttering among relatives of preschool-age children who stutter to avoid the undersampling of females due to their higher tendency for spontaneous recovery and to avoid the any bias obtained from only studying adults. They obtained detailed pedigrees (including first, second and third-degree relatives) for 69 children from one or both of their biological parents. 49 of the 69 probands (71% of the sample) had a positive family history of stuttering. Of the 49 positive history probands, 37 (76%) were male and 12 (24%) were female. Their segregation analyses found statistical evidence for transmission of a single major locus in the inheritance of susceptibility for stuttering. Janssen and colleagues found similar results in their 1996 study with 106 adult probands.

A different variation on previous twin studies was conducted by Dworzynski and colleagues in 2007 to identify if genetic factors contributed to persistence and recovery from stuttering. Using data from the Twins Early Development study, which consisted of parental reports regarding stuttering collected at ages 2, 3, 4 and 7, Dworzynski et al.(2007) identified children who had recovered and those who persisted. Out of 12,892 children, 950 children had recovered by the age of seven and 135 persisted. They performed logistic regression analysis to test whether stuttering at early ages were predictive of stuttering in following years. They found that reports of stuttering at ages 3 and 4 predicted stuttering at age 7; while reports of stuttering

at age 2 did not. Dworzynski and colleagues again identified that concordance rates for stuttering were consistently higher for monozygotic twins for all ages and for both recovery and persistency than for dizygotic twins. Their conclusions are that significant genetic influences but "no shared environmental influences" influence susceptibility to stuttering at ages 3, 4, and 7, but did not identify significant differences in heritability for persistence and recovery groups.

Following up on the strong evidence for genetic inheritance in epidemiology studies, more recent work has focused on identifying specific genes that may be responsible for liability to stuttering through DNA linkage analysis. Shugart et al. (2004) conducted a genome-wide linkage analysis using 392 markers across the genome in 226 individuals in 68 families, 188 of whom with a history of stuttering. They identified several moderate signals across chromosome 18 and weak signals from chromosomes 1, 2, 10 and 13. Riaz et al. (2005) performed a genome-wide linkage analysis in 44 Pakistani families with a history of stuttering that included individuals with a history of stuttering as well as their parents (a total of 199 genotyped individuals, 144 affected and 55 unaffected). They identified linkage evidence on chromosomes 1, 5, and 7 with a very strong signal on chromosome 12.

Suresh et al. (2006) reported findings of a genome-wide scan analysis in 100 families with at least two relatives affected with stuttering. The families included 252 individuals with persistent stuttering, 45 who recovered from stuttering, and 19 individuals who were too young to be identified as recovered or having persistent stuttering. Genome-wide linkage analysis of 100 families indicated evidence for linkage (largest signal) on chromosome 9, and modest signal on chromosomes 2 and 7. They identified modest evidence for linkage with persistent stuttering on chromosomes 15 and 13. Suresh et al. further found genome-wide significant evidence for linkage of stuttering in the female-only subgroup on chromosome 21; but as for the male-only

subgroup, they found moderate evidence for linkage of stuttering on chromosomes 7 and 20. Together with other studies (e.g. Wittke-Thompson et al., 2007), consistent evidence of genetic linkage in PDS has emerged. Definitive evidence for a single major gene locus is not available yet, but several candidate genes of varying influence appear to increase a liability to stuttering. Identifying the candidate genes is only part of the process though, because the role that candidate genes have in development and in speech-language production still have to be understood.

Influence of genes on the neuroanatomy

We predict the genetic disposition to stuttering is expressed at least partly in the neural control of speech production. It is likely that a genetic predisposition to stuttering could be expressed as difference in the brain development in speech production system because it has been shown that genetic differences present themselves as differences in the brain anatomy. The initial work by Thompson et al. (2001) demonstrated that individual genetic differences have significant impact on brain structure. Genetic relationships show increasingly similar neuroanatomy, more specifically, Thompson et al. found that the genetic factors significantly influenced important speech and language regions, Broca's and Wernicke's areas, as well as other frontal regions in the cortex. Peper, Brouwer, Boomsma, Kahn & Hulsoff Pol (2007) reviewed brain imaging studies in twins and identified that human brain structure is genetically influenced. They revealed high heritability estimates of neural structures for gray matter density in important speech and language related regions such as medial frontal cortex, Heschl's gyrus, Broca's area, anterior cingulate, and hippocampus. Various other researchers have looked at the relationship between genes and brain structure in adults, children and monozygotic and dizygotic twins and they identified that the variation in gray matter and white matter volume of human brain is primarily genetically determined (Gilmore et al., 2010; Hulshoff Pol et al., 2006; Wright,

Sham, Murray, Weinberger & Bullmore, 2002). Along with the accumulating evidence regarding the genetic basis for stuttering, the strong evidence for the genetic and neuroanatomical relationship can shed light on the heritability of linguistic skills and the genetic predisposition for disorders that affect the anatomy of the human brain.

Neuroimaging studies and Stuttering- Evidence from functional brain imaging

The strong evidence supporting stuttering as a disorder that is in part genetically determined and that genes have significant influence to brain structure has been influential in shifting the focus of research away from environmental and psychological theories toward ways of conceptualizing and identifying the biological mechanisms that can explain stuttering. Accumulating evidence points to prominent neural differences in people who are affected by stuttering that additionally support a biological explanation.

Acquired stuttering due to a brain injury or stroke presents evidence that brain systems may mediate stuttering. Van Borsel, Van Lierde, Van Cauwenberge, Guldemont & Van Orshoven (1998) presented a case report of a 69- year-old right handed male with no history of speech or language disorders. He began complaining about "stutter-like speech" 1 month after a stroke that was accompanied by speech deterioration. Four months post-stroke, he showed severe stuttering. Van Borsel et al. claimed that a lesion to the left supplementary motor region may have caused the severe stuttering. Van Borsel et al. presented another case report about a 38-year old right handed male who did not have a history of speech and language deficits (2003), but developed cognitive problems, language problems and severe stuttering in propositional speech six months after an ischemic lesion to the left thalamus. Franco et al. (2000) also presented a case report of a 53-year-old right handed male who had a cortical infarct on the left pre-central

circumvolution. The lesion did not induce aphasia or any neurological deficits other than stuttering characterized by blocks, repetitions at word-initial level.

Case studies of lesions reveal patterns of deficits that can lend evidence to theories of brain function and disorders but cannot be studied prospectively and are not replicable. Modern brain imaging that includes both whole-brain anatomical and functional imaging now allows for inferential studies of brain structure and function in healthy and disorder populations.

Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI). PET technology relies on the assumption that an increase in the brain activity is reflected by increased blood flow to the active area. Injection of radioactively tagged isotope enables detection of increased blood flow in a given area as the PET scanner can track the radioisotope's concentration in a brain region. fMRI is a later developed variant of MRI which measures changes in blood oxygenation. Increased neuronal activity leads to changes in oxygen metabolism that invokes higher blood flow to the active region and changes the balance of oxygenated and deoxygenated blood. fMRI has better resolution than PET and is non-invasive, so, it represents much less risk to participants than PET. Now, fMRI paradigms have been developed that are less sensitive to movement artifacts, which permits functional imaging of ongoing speech production.

Fox et al. (1996) investigated neural systems of stuttering by a PET study in 10 male AWS and 10 male controls matched for age and handedness. They had three separate PET scans (40 seconds each) in the following conditions: chorus reading, solo reading, and eyes-closed rest. Prominent differences between solo reading and choral reading conditions were found for the AWS in terms of increased activation and deactivation in both hemispheres. During solo reading

condition, AWS had widespread overactivation of motor system areas in right hemisphere, rather than left, in both cerebrum and cerebellum as opposed to left hemisphere activity in controls. In addition, AWS showed relative deactivation of left hemisphere auditory areas, which are related to auditory self-monitoring. Further deactivation in frontal-temporal regions that are typically activated in speech tasks was also noted in AWS during solo reading. During choral reading on the other hand, Fox et al. observed these abnormal patterns of overactivation and deactivation were significantly decreased. The authors concluded that stuttering results from a right dominance of the cerebral speech motor system, a lack of self-monitoring of speech production, and an over-activation of the speech motor system. This early paper may have over-estimated the causal relationships between the findings and the cause of stuttering, but it confirmed there are neurological correlates of this disorder.

Soon after the Fox et al. study, Braun et al. (1997) reported PET results in 18 AWS and 20 controls during speech and language tasks. They found that during structured sentence production and conversational speech tasks, AWS demonstrated either absent, bilateral or right-lateralized activation patterns as opposed to left-hemisphere activation in controls. These significant differences were present even though the stuttering participants produced these utterances fluently. Therefore, the authors speculated that cerebral hemispheric regions related to speech production may be different in AWS even in the absence of stuttering. When they compared activity in this fluent speech condition with conditions where speech was more disfluent, AWS demonstrated over-activation of the anterior forebrain region. This over-activity was expressed in motor areas which contrasted with relatively depressed in post rolandic regions which are associated with perception and decoding of auditory information. Braun et al. concluded that left-hemisphere activity might have a significant role in the production of

stuttered speech, while the activity in the right hemisphere may be due to a compensatory process to avoid stuttering.

Fox et al. (2000) later investigated neural correlates of fluent speech and stuttering by comparing disfluency counts and syllable rate in oral reading and choral reading tasks. They re-analyzed the PET scans from the earlier study (Fox et al., 1996). The results indicated stuttered speech was significantly lateralized to the right cerebral and left cerebellar hemispheres; while stutter-free speech was biased towards the left cerebral and right cerebellar hemispheres. They identified that stuttered speech occurred in speech-related regions, involving the mouth representation in motor cortex, Broca's area, supplementary motor area, anterior insula and the cerebellum.

Stager, Jeffries & Braun (2003) investigated the neural mechanisms with PET that are involved when fluency is induced in people who stutter. 17 adults with persistent developmental stuttering and 17 controls were scanned during two fluency evoking conditions, two disfluency-evoking conditions and rest. The results showed that activation in auditory association areas involved in speech processing and motor regions involved in control of speech articulators was greater during fluency inducing tasks than during typical speech that is more susceptible to disfluency. Stager et al. concluded that fluent speech might require more effective auditory motor coupling.

Chang, Kenney, Loucks & Ludlow (2009) conducted an fMRI study in 20 AWS (9 females) and 20 controls (11 females). They investigated activation patterns in perception, planning, and fluent production of both speech and non-speech gestures and also between females and males. The results indicated that during perception and planning, people who stutter

had less activation in the frontal and temporoparietal regions than controls for both speech and non-speech tasks. Whereas during production of speech and non-speech gestures, participants who stutter had less activation in the left superior temporal gyrus and left pre-motor areas, but greater activation in the right superior temporal gyrus and greater activation in Heschl's gyrus, insula, putamen, and precentral motor regions bilaterally. Chang et al. reported that these atypical brain activity patterns in the stuttering group were greater in adult females. Because the aberrant activation in the stuttering group could be observed in both tasks, Chang et al. concluded this activation might not be speech specific.

Brown, Ingham, Ingham, Laird, and Fox (2005) reported an important meta-analysis of brain imaging studies of adults with persistent developmental stuttering. This analysis directly used imaging data from the relatively numerous previous studies to isolate areas that are most consistently associated with stuttering. They performed two parallel analyses; one investigating stuttered production in people who stutter and the other looking at brain activation patterns of fluent speech in controls. The results revealed that typically fluent subjects show significant activation patterns in primary motor-cortex, premotor cortex, Rolandic operculum, supplementary motor area, auditory areas and lateral cerebellum. Even though roughly similar brain areas were activated in people who stutter, the activation patterns were significantly different from controls in several aspects. AWS showed significantly higher activity in motor areas including primary motor cortex, cingulate motor area, cerebellar vermis and supplementary motor area (SMA). They also demonstrated aberrant right-lateralization in Rolandic operculum and anterior insula. The other very significant finding was the absence of significant bilateral activations in auditory areas in AWS when hearing their own speech.

Neuroimaging studies and Stuttering- Evidence from structural brain imaging studies

The accumulating evidence from functional imaging studies showing aberrant activity patterns in language-related brain regions of AWS has been followed up by investigations of structural differences in the brains of people who stutter. A number of researchers have identified significant anatomical and structural differences between people who stutter and fluent speakers (Beal, Gracco, Lafaille & De Nil, 2007; Chang et al., 2008; Cykowski et al., 2008; Foundas, Bollich, Corey, Hurley & Heilman, 2001; Foundas et al., 2003; Jancke, Hanggi & Steinmetz, 2004; Lu et al., 2010; Sommer et al., 2002). Refer to *Table 1* for a summary of the findings of these studies. Foundas and colleagues (2001) investigated anatomical differences in AWS by manually tracing anatomical regions in MRI scans and comparing these regions with controls. Foundas et al. measured frontal areas including pars triangualris and pars opercularis; and temporo-parietal areas including planum temporale and posterior ascending ramus in both hemispheres. They found that AWS had significantly larger planum temporale in both hemispheres. The planum temporale is typically larger in the left hemisphere and is considered a marker of language laterality. AWS showed reduced asymmetry which provided some evidence for the hypothesis of reduced language lateralization in stuttering. In addition, they found significantly more gyri along the superior bank of the sylvian fossa in people who stutter. Foundas et al. (2001) concluded that anomalous anatomy in the perisylvian speech and language areas might "put an individual at risk for the development of stuttering".

In a follow-up study, Foundas and colleagues (2003) used structural MRI to measure prefrontal and occipital lobe volumes and compare whether these measures were associated with stuttering severity and language abilities in 16 AWS and 16 matched controls. In this blinded study, Foundas et al. did not find significant hemispheric and total brain volume differences

between the two groups. However, the results indicated larger right prefrontal and larger right occipital lobe volume in controls while AWS did not have these asymmetries.

More recently, Cykowski and colleagues (2008) reported that perisylvian sulcal morphology showed a small but significant increase in the number of sulci which connects the second segment of the Sylvian fissure in the right hemisphere in people who stutter. In addition, people who stutter had a similar increase in the number of the "suprasylvian gyral banks" along the Sylvian fissure in the right hemisphere, while no such differences were noted in the left perisylvian region. Their findings differed from Foundas et al. (2003), in that cerebral anatomy measures did show asymmetry differences in frontal and occipital lobe, planum temporal and Sylvian fissure regions among AWS compared to controls. These morphometric analysis studies required manual tracing of a few regions in the brain which is labor-intensive and may be difficult to replicate, which then leads to low intra- and inter-rater reliability (Watkins et al., 2001).

Diffuse Tensor Imaging (DTI) Findings

Sommer and colleagues (2002) investigated the neuroanatomical basis of PDS in 15 AWS and 15 matched controls with a form of MRI known as diffusion tensor imaging (DTI). Diffusion tensor imaging is also a popular method to investigate the neuroanatomical differences. White matter fascicle can be visualized and characterized in two and three dimensions using diffusion tensor imaging (Assaf and Pasternak, 2008). They found reduced fractional anisotropy of white matter in the left rolandic operculum (an area close to the portion for laryngeal and tongue representation in the motor strip) in AWS. This finding is significant because the arcuate fasciculus the linking Broca's and Wernicke's areas pass through this region. Sommer et al. concluded that the reduced white matter anisotropy in these areas in the left

hemisphere might cause decreases in signal transmission and a disruption in sensorimotor integration for fluent speech production.

Chang et al. (2008) also used DTI method to compare white matter volumes in 3 groups of children: 8 with persistent stuttering, 7 recovered children and 7 fluent control children. The DTI results indicated that both the persistent stuttering and recovered groups had reduced white matter volume in the left rolandic operculum, which is proximal to and may include orofacial motor representations. In addition, DTI results suggested there was reduced left white matter anisotropy underlying motor regions for face and larynx in the persistent stuttering group. This study is important as it was the first to document neurological differences in children with persistent stuttering and those who have recovered.

Voxel-Based Morphometry (VBM) as a Method

In contrast to manual tracing, other structural analysis methods, such as diffusion tensor imaging and voxel-based morphometry (VBM), allow automate, and reproducible whole-brain structural imaging (Ashburner & Friston, 2000). Investigation of the whole-brain; as opposed to a few regions of interest (ROIs); can allow an unbiased analysis where one can compare each point in the brain at equally high-spatial resolution. VBM analysis procedures are discussed in *Methods* chapter. Both DTI and VBM have identified differences in persons who stutter.

VBM Investigations of stuttering

Before reviewing VBM studies of stuttering, it is relevant to note that the VBM has identified significant brain volume changes in various studies including investigations of aging differences (Good et al., 2001) and developmental disorders such as autism (Craig et al., 2007), and schizophrenia (Di, Chan & Gong, 2009; Kubicki et al., 2002). VBM has also been used to

investigate the neuroanatomical underpinnings of various speech and language disorders such as dyslexia (Steinbrink et al., 2008), specific language impairment (SLI) (Watkins et al., 2002), and aphasia (Gorno-Tempini et al., 2006).

Jancke and colleagues (2004) were the first to report use of VBM to test for structural markers of stuttering in 10 AWS and 10 controls, comparing gray and white matter volume. An increased volume of white matter was found in the right hemisphere including the superior temporal gyrus (including the planum temporale), the inferior frontal gyrus (including the pars triangularis), the precentral gyrus close to the regions for face and mouth movement representation, and the anterior middle frontal gyrus in people who stutter. In contrast, the control group had greater white matter asymmetry favoring the left auditory cortex as opposed to the greater symmetry across the left and right auditory cortices in AWS. Jancke et al. reported that the anatomical differences between AWS and controls were more widespread (in perisylvian speech and language areas as well as in prefrontal and sensorimotor areas) than had been reported in previous studies of structural neural differences in people who stutter. The authors suggested that the question of whether these anatomical differences are the cause or result of stuttering yet remained unanswered.

Beal and colleagues (2007) conducted a similar VBM study in 28 male AWS and 28 controls. They found AWS expressed significantly increased gray matter volumes in widespread areas: right and left superior temporal gyri, left inferior frontal gyrus, right precentral gyrus, left middle temporal gyrus and at the level of right cerebellar tonsil. No areas of increased gray or white matter density were reported for the control group. They concluded that their findings presented evidence for acquired or congenital brain differences in gray and white matter volumes

in people who stutter, similar to findings from previous studies (Foundas et al., 2001, 2003; Sommer et al., 2002).

Chang et al. (2008) used VBM to compare gray matter volumes in 3 groups of children: persistent stuttering, recovered children and fluent controls. Chang et al. noted reduced gray matter volume in speech-related regions including the left inferior frontal gyrus and bilateral temporal regions in both the persistent stuttering and recovered groups. A comparison of the persistent stuttering and recovered stuttering groups revealed that the children with persistent stuttering had greater gray matter volume in both the left and right superior temporal gyrus (STG). They speculated that the increased gray matter volume in the STG bilaterally for children with persistent stuttering might be due to chronic stuttering. Unlike previous studies, Chang et al. did not find evidence of greater right-left asymmetry in these groups. They presumed that the right-hemisphere structures of adults may account for neuroplasticity resulting from long term chronic stuttering.

Another VBM study investigating anatomical differences between PWS and fluent speakers was conducted by Lu et al. (2010) with 12 AWS and 12 matched controls. AWS had increased gray matter volume in areas that are responsible for motor-speech coordination. AWS demonstrated decreased gray matter volume in the vicinity of Broca's region, left superior temporal gyrus, right middle temporal gyrus, and right cerebellum. In addition, Lu et al. reported that AWS had greater white matter volume in areas underlying the right inferior and superior temporal gyri, and left cerebellum and they demonstrated less white matter concentration in the right precentral gyrus, left superior temporal gyrus, and bilateral cerebellum. The authors proposed that disrupted communications among a widely distributed neural network in the left hemisphere and basal ganglia circuits might result in developmental stuttering.

Statement of purpose and hypotheses:

The evidence from functional imaging and structural imaging studies suggests that PWS appear to differ from PWNS in both brain function and anatomy in areas involved in sensorimotor integration for speech production. PWS demonstrated unusual activation patterns during speech in areas encompassing the temporal-parietal and frontal speech motor regions, with a tendency for more activation in the right hemisphere. Anatomically, these areas correspond to auditory association cortices and the perisylvian / inferior frontal regions, which have also been reported to have more variable neuroanatomy in PWS. Studies of anatomical morphometry and white matter diffusion properties suggest there are morphological and structural connectivity differences between PWS and PWNS within and between these regions also.

Therefore, the purpose of this study is to investigate whether volumetric measures of neural tissue in speech relevant brain regions differentiate AWS and CWS from normally fluent speakers and whether brain structure differences in children who stutter are related to adult patterns. A comparison of AWS and CWS using VBM has not been reported previously. Figures 1 and 2 illustrate, in a **schematic format**, the general pattern of differences that have been reported between control speakers, children who stutter and adults who stutter (for simplicity control speakers are not separated into age groups). Following these reports, we predict that brain areas involved in speech sensorimotor integration for speech production will be structurally different in persons who stutter in terms of both gray matter and white matter volume concentration and may follow the patterns in *Figures 1 and 2*.

However, the data from the single comparison of children (Chang et al., 2008) and the adult studies present conflicting evidence regarding the volumetric density of the structures involved. Clearly, previous studies indicate adults who stutter show *increased* gray matter and white matter volumes in speech areas compared to fluent controls. On the other hand, children who stutter showed *reduced* gray and white matter volumes as opposed to controls. It is possible these conflicting findings are due to factors such as different MRI scanning protocols and different data processing approaches, but these are still unlikely to account for the different direction of group differences in these previous VBM studies. Are these differences possibly related to development or subject selection? Certainly, recovery is not an issue because the children in Chang et al. study (2008) showed persistent stuttering. The process that leads from *reduced* volume of gray and white matter in childhood to *increased* tissue density in adulthood remains enigmatic. We expect that the current study may resolve the conflict between previous reports by comparing the brain volume of gray and white matter between children and adults. Although there is concern that the brains of children are too variable in size and shape to be compared directly with the adult brain, previous reports which assessed the feasibility of such a comparison demonstrated that pediatric brains (6 years of age and older) and adult brains can be placed into a standard stereotactic space with comparable reliability (Burgund et al., 2002; Kang, Burgund, Lugar, Petersen, Schlaggar, 2003; Muzik, Chugani, Juhasz, Shen, Chugani, 2000; Schlaggar et al., 2002). Evidence on the feasibility of comparison of child brain with adult brain will be discussed in the *Methods* section.

Following Chang et al. (2008), we might expect to find *reduced* gray and white matter density in children and adults who stutter compared to controls. Since children are included along with adults in the present study, we aim to test the hypothesis of whether there is indeed a

differential pattern of change in relative tissue proportions from childhood to adulthood in persons who stutter – i.e., less gray matter than normally fluent in childhood increasing to more gray matter in adulthood compared to normally fluent. It is important to mention that the MRI data from the children was collected as part of a previous dissertation and reported by Chang et al., (2008). This study differs considerably as comparisons between adults and children will be the focus rather than comparisons of children, although we will attempt to replicate the analyses reported by Chang et al (2008). We also note that Chang et al did not report a comparison of white matter volume which will be completed in this study.

CHAPTER III: METHODS

Participants

The data used in this study come from the participant pool of the Stuttering Research Project, an on-going longitudinal study in the Department of Speech and Hearing Science. The children data has also been presented in a previous dissertation in the same department.

Adults: A total of 11 male AWS and 25 male AWNS between 20-35 years of age were recruited as part of an ongoing study using advertisements or by referral from the University of Illinois Speech and Hearing Language Pathology Clinic. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). A diagnosis of persistent stuttering was confirmed in the experimental group by a clinically certified speech-language pathologist with expertise in stuttering. In all cases, overt stuttering was observed by one of the investigators.

The mean score of self-reported stuttering severity among the AWS was 3.66, (sd 1.61) on a scale from 0 (no stuttering) to 7 (very severe stuttering), indicating severity ranged from mild to moderate. Each AWS reported previous therapy for stuttering, but only two individuals were receiving therapy at the time of the study. Eight of the AWS showed greater than 3% stuttering-like disfluencies (SLD) (Yairi & Ambrose, 1992) during reading and conversational speech and reported a history of stuttering since early childhood. The remaining stuttering participants could not return for disfluency analyses, but each was observed to stutter by a speech-pathologist experienced in stuttering. Otherwise, the stuttering and normally fluent participants reported a negative history for neurological, psychiatric, speech, hearing and/or other

language disorders. The methods of this study were approved by the Institutional Review Board at the University of Illinois at Urbana-Champaign.

Children: All subjects were right-handed males between 8 and 13 years of age. One group consisted of children (n=7) who had once stuttered but had recovered naturally (CWRS), another group of children (n=8) with persistent stuttering (CWPS), and a control group (n=7) of normally fluent children (CWNS). All subjects were matched in age. Inclusion criteria required a negative history for speech and language deficits based on standardized speech and language testing including: Expressive Vocabulary test (EVT) (Williams, 1999), Peabody Picture Vocabulary test (PPVT) (Dunn, 1959), Test of Oral Language Development (TOLD-I:3) (Newcomer and Hammill, 1992). In addition, the rigorous subject-selection criteria included not presenting with any type of behavioral, cognitive, or neurological disorders (i.e. learning deficit, attention deficit hyperactivity disorder, and dyslexia). The mean score of stuttering severity of children with persistent stuttering was 2.38 (sd 0.74). Recovered children had stuttered between the ages of 2 and 3 years and participated in a longitudinal study of early preschool childhood stuttering at the University of Illinois and were followed every 6 months until the time of recovery, usually 2-3 years post-onset (Ambrose and Yairi, 1999).

Imaging

All images were collected on a 3T Siemens Magnetom Allegra MR Headscanner at the Biomedical Imaging Center of the Beckman Institute at the University of Illinois, Urbana-Champaign. High resolution anatomical volumes encompassing the cerebrum and cerebellum were collected using a T1-weighted MPRAGE (magnetization-prepared rapid acquisition gradient echo) sequence (sagittal slice volume=196, TR=1600ms, TE=2.22ms). To minimize

head movements, participants' heads were padded with foam and lightly held in place with a strap across the forehead. Participants were asked to hold their head still during the scan. Some of the adult participants and all children viewed a movie of their choice though MRI compatible goggles. They wore earplugs to mask scanner noise and headphones to hear the movie.

VBM Analysis Procedures

Voxel-based morphometry (VBM) involves a voxel-wise comparison of the local concentrations of white and gray matter between groups of subjects under consideration. All the structural images were checked for artifacts and images with poor resolution; or low-contrast were eliminated. Some images were adjusted to have the center point on the anterior commissure for all images (Good et al., 2001). Ashburner and Friston (2000) described VBM analysis procedures in detail. See *Figure 3* for VBM processing steps. The VBM processing steps involving spatial normalization, segmentation, smoothing, and statistical analysis were conducted using MATLAB 5.3 (Mathworks, Natrick, MA) and SPM5 (statistical parametric mapping) (Wellcome Trust Center for Neuroimaging, London; (Ashburner & Friston, 2000). A detailed description of these steps is also available in the SPM5 manual (http://www.fil.ion.ucl.ac.uk/spm/) (Ashburner, 2006).The first step in the VBM involved spatial normalization to the same template in which individual volumes were co-registered to a common stereotactic space (template) to accommodate for individual differences in brain size. Spatial normalization is a computer-based, automated procedure (Abell et al., 1999).

In the current study the images from both adults and children groups were registered to the same adult template. Previous reports have demonstrated that comparing child brains (older than 6 years of age) to adult brain is feasible because the only small anatomical differences do

not preclude registration to a common stereotactic space (Muzik et al., 2000; Burgund et al., 2002; Schlaggar et al., 2002; Kang et al., 2003). Muzik et al. (2000) assessed the use of and reliability of SPM for child brain to adult brain comparisons and concluded that even though the error associated with spatial normalization of pediatric brains (ages 6 to 14 years) to an adult template was higher than in adults, this error did not result in artifacts in the SPM analysis. Various studies have proven the feasibility of direct statistical comparisons of school-age children brain (7 years and older) to adult brain by spatial normalization to the same stereotactic space.

Following spatial normalization, the images were segmented into three tissue classes (gray matter, white matter, and cerebrospinal fluid (CSF) using an automated Bayesian algorithm (Ashburner & Friston, 2000). During the segmentation procedure, voxel intensities that match that of the three different tissue types are identified and continuous probability maps are created (Salmond et al., 2002). This tissue-segmentation procedure is automated and is free from subjective identification of tissue boundaries, which has been suggested as a problem in methods where tissue boundaries are identified though manual tracking (Watkins et al., 2001). While during spatial normalization some brain regions are expanded or contracted, during modulation step the images are scaled by the amount of contraction, in order to enable the total amount of white matter or gray matter in the modulated gray or white matter remains the same as in the original images. The segmentation and modulation are actually processed simultaneously in SPM 5 using a unified segmentation algorithm (Ashburner & Friston, 2005).

The segmentation of the images into three different tissue types was followed by a smoothing procedure which created individual three dimensional intensity maps of the three tissue types (Good et al., 2001). The smoothing procedure utilized an 8 mm FWHM isotropic

Gaussian smoothing model kernel, which leads the data to conform more closely to the Gaussian field model underlying the statistical procedures used for making inferences about regionally specific effects. In addition, the data is conditioned to be more normally distributed (by the central limit theorem) as a result of smoothing procedure (Good et al., 2001). The smoothing procedure produces voxel values derived from the weighted values of the signal in each voxel and its neighbors, which reflects the amount of particular tissue type, its regional density, within the smoothing kernel (the size of the region is defined by the size of the smoothing kernel; 12-mm, or 8-mm (Ashburner & Friston, 2001; Watkins et al., 2001).

Following the completion of the automated smoothing procedure, the voxel values of each tissue type (gray matter or white matter) are compared separately. A statistical comparison of individual tissue densities results in a statistical parametric map (SPM) in which each voxel has an associated inferential statistic and distribution (Abell et al., 1999).

The whole brain group comparison was conducted with two sample t-tests with an absolute threshold mask of $p < 0.005$ (uncorrected) and a threshold of >30 voxel clusters. For these pair-wise comparisons, the factor was group (stuttering vs. control in adults; and persistency vs. recovery vs. control in children). Ashburner and Friston (2000) reported that uncorrected values do not severely compromise the statistical analysis. Uncorrected statistical values have been reported in previous VBM studies for stuttering (Chang, et al., 2008; Beal et al., 2007) and in reports of normal population (Wilke, Krageloh-Mann, Holland, 2007) and various clinical populations such as Alzheimer's disease (Thomann, Toro, Santos, Essig, Schroder, 2008), Parkinson's disease (McKeith, Burn, Williams, O'Brien, 2004), and schizophrenia (Mane et al., 2009).

CHAPTER IV: RESULTS

Pair-Wise Contrasts

Individual pair-wise t-tests were carried out to assess gray and white matter regions that differ in volume between two groups. A voxel cluster threshold size of >30 was applied to all the resultant statistical parametric maps (SPMs) at a *p* value of 0.005 (uncorrected). Each pair-wise contrast produced two SPMs; in adults, for example, one SPM indicates clusters where AWS > AWNS and the second SPMs indicates where AWNS > AWS for a whole brain contrast of gray matter volume. A corresponding comparison of white matter generated a similar set of contrasts. The lists of regions of gray and white matter that differed significantly between the adult groups based on pair-wise contrasts are presented in *Tables 2-3*. The tables showing contrasts between the child groups are numbered 4-11 in *Tables* section.

AWS versus AWNS

Gray Matter

Figure 4 shows the pair-wise gray matter contrasts between AWS and AWNS. Many of these areas showed group differences bilaterally (see *Table 2*).The bilateral areas where AWS group showed significantly more gray matter volume than AWNS include putamen and thalamus, postcentral gyrus, superior frontal gyrus and middle frontal gyrus. Particular unilateral areas where AWS showed increased gray matter volume than AWNS include the left middle temporal gyrus and right precentral gyrus. There were relatively fewer regions in which the AWNS had significantly higher gray matter volume, which included the right inferior parietal lobule, left postcentral gyrus, and the left cerebellar hemisphere.

White Matter

The AWS only had significantly greater white matter volume in the left anterior cingulate (*Table 3, Figure 5*). AWNS group showed significantly greater white matter volume than the AWS group in the bilateral middle temporal gyrus, bilateral STG, bilateral precentral gyrus, right supramarginal gyrus (SMG), right inferior parietal lobule, and right postcentral gyrus. Other regions involved the cerebellum including posterior cerebellar tonsil on both hemispheres, left posterior cerebellar tuber, and left posterior cerebellar pyramis.

VBM Comparison of Gray Matter and White Matter in Children

The same pair-wise contrast approach and threshold (> 30 voxels at $p < 0.005$) was used to compare the three groups of school-age children.

Ever Stuttered versus CWNS

The first contrast included children who were persistent in (CWPS) and recovered from stuttering (CWRS) groups within a single group of 'ever stuttered' to compare whether a history of stuttering altered gray and white matter volumes in comparison with normally fluent children group (CWNS) (see *Tables 4 and 5*).

Gray matter

Ever stuttered children only showed significantly more gray matter volume than normally fluent children in the right parahippocampal gyrus. Other relevant regions for speech production and perception did not reach the cluster size of 30 voxels but did show significantly higher gray matter volume. These regions encompassed the left middle temporal gyrus (MTG), right precentral gyrus (PrCg), and right temporal lobe regions. The Ever Stuttered group had

significantly less gray matter volume than CWNS in regions such as the bilateral superior and middle frontal gyri, left supramarginal gyrus (SMG), and right cingulate gyrus (See *Table 4*).

White Matter

Regions with significantly more white matter volume in the Ever Stuttered child group included regions such as the left inferior parietal lobule, left parahippocampal gyrus, and right precuneus, as well as the left inferior semi-lunar lobule, and right uvula in the cerebellum. Other clusters proximal to language relevant regions such as the left insula, , left cingulate gyrus and right middle temporal gyrus had higher white matter volume but did not reach significance the >30 voxel cluster threshold (See *Table 5*). The Ever Stuttered group exhibited significantly less white matter volume than normally fluent children in the right postcentral gyrus, right inferior temporal gyrus, and right middle frontal gyrus.

CWPS versus CWNS

Gray Matter

Children with persistent stuttering showed significantly more gray matter than their normally fluent peers (CWNS) in areas such as left postcentral gyrus, left inferior frontal gyrus, and right cuneus (see *Table 6* and *Figure 6*). Areas with significantly less gray matter volume in CWPS group compared to CWNS include the left precentral gyrus, left paracentral lobule (supplementary motor area), left caudate, right inferior parietal lobule, left superior frontal gyrus and bilateral middle frontal gyrus. Other areas including the posterior cerebellar tonsil, and left middle temporal gyrus did not reach the significance criteria of >30 voxel cluster size but had significantly higher volume ($p < 0.005$).

White Matter

CWPS group had significantly more white matter volume than their normally fluent peers (CWNS) in a number of regions proximal to the right middle temporal gyrus, right posterior cerebellar declive, left inferior parietal lobule, and bilateral precuneus (see *Table 7*). Children with persistent stuttering exhibited significantly less white matter volume than CWNS proximal to the left precentral gyrus, right middle frontal gyrus, and right superior parietal lobule. Other areas with significantly less white matter volume, including white matter close to the right middle temporal gyrus, right postcentral gyrus and anterior cerebellar culmen, did not meet the 30 voxel cluster threshold (*Table 7*).

CWPS versus CWRS

Overall, children with persistent stuttering showed significantly less gray and white matter volume compared to children who recovered from stuttering.

Gray Matter

CWPS only had significantly more gray matter volume than CWRS in the left cingulate gyrus (*Table 8*). The CWRS group, in contrast, showed increased gray matter volume in numerous areas. This set of regions included left anterior cingulate, left posterior cerebellar declive, right middle temporal gyrus, right fusiform gyrus, right inferior frontal gyrus, and bilateral left middle frontal gyrus, (See *Table 8* and *Figure 7*). Other regions which approached the 30 voxel cluster threshold were the left superior temporal gyrus, left supramarginal gyrus, right anterior cerebellar culmen, and right postcentral gyrus.

White Matter

Regions with significantly more white matter volume in the CWPS group compared to CWRS group only include cerebellar regions such as the posterior cerebellar declive, and posterior cerebellar tonsil. CWPS showed significantly less white matter volume than CWRS in areas such as left inferior frontal gyrus, left cerebellum, right posterior cerebellar tonsil, right medial frontal gyrus and bilateral superior frontal gyrus (See *Table 9* and *Figure 7*).

CWRS versus CWNS

Gray Matter

Areas of significantly more gray matter volume in CWRS than CWNS included the left middle temporal gyrus, left inferior occipital gyrus, right middle frontal gyrus, and bilateral posterior cerebellar declive, (See *Table 10*). The CWRS had significantly less gray matter volume than their normally fluent peers in areas including the left middle frontal gyrus, and right cingulate gyrus (*Table 10*).

White Matter

The CWRS group exhibited significantly less white matter volume than CWNS in regions such as the right precentral gyrus, left posterior cerebellar uvula, and right posterior cerebellar tuber (*Table 11*). Some of the regions where CWRS had significantly more white matter volume than CWNS included right superior temporal gyrus, right inferior parietal lobule, right superior frontal gyrus, right medial frontal gyrus, and cerebellar regions such as right posterior cerebellar tonsil and right posterior cerebellar pyramis (*Table 11*).

Similarities and Differences between Child Data and Adult Data in the present study

Our analysis focused on statistical differences between the children groups as we continue to resolve problems in comparing the adult and children groups. However we will descriptively compare the patterns of results in our child data and adult data (See *Figures 8 & 9*).

Gray Matter Findings

The overall finding from gray matter comparisons was that compared to normally fluent children, the combination of persistent and recovered groups showed significantly less gray matter volume in areas such as middle frontal gyrus in right and left hemispheres, left supramarginal gyrus, right cingulate gyrus, right and left superior frontal gyrus, and right postcentral gyrus. Compared to controls and persistent group, the recovered group had intermediate levels of gray matter volume. An interesting finding was that AWS showed significantly increased gray matter volume compared to AWNS in all of these regions whereas the ever-stuttered children group had less gray matter volume than normally fluent children (See *Figure 8*).

The finding that the areas where persistent group had significantly less gray matter volume than the recovered and control groups are the regions where AWS have increased volume compared to adult controls is very much in agreement with our initial hypothesis that for people who stutter, there seems to be a process that leads from reduced volume of gray matter in childhood to increased tissue density in adulthood. The gray matter volume results in various regions in the cerebellum were an exception to this prediction. AWS showed reduced gray matter volume in cerebellum (left hemisphere), and similarly, children with persistent stuttering exhibited significantly less volume in left cerebellum compared to CWRS and CWNS groups.

On the other hand, recovered children showed significantly more gray matter volume than CWNS in the left cerebellum regions. Implications of these findings will be discussed in a separate section on recovery and persistence.

The recovered group showed more gray matter than CWPS and CWNS in regions such as left and right middle frontal gyrus, bilateral superior frontal gyrus, right and left middle temporal gyrus, and right inferior frontal gyrus, but reduced gray matter volume compared to the other groups in bilateral cingulate gyri. Contrary to the reduced volume in cingulate gyrus in CWRS and CWPS groups, AWS had significantly more gray matter volume than AWNS in left posterior cingulate gyrus and right anterior cingulate gyrus.

Another interesting finding was that the balance of structural differences in adults and children differed. The gray matter volume differences in subcortical regions between AWS versus AWNS were more prominent than the differences found in cortical regions. In children however, differences in cortical areas between stuttering and non-stuttering children comparisons were greater for the cortex. Compared to controls, while AWS showed increased gray matter in subcortical areas such as bilateral putamen, bilateral thalamus and cingulate gyrus; CWPS and CWRS had reduced gray matter volume in subcortical areas including caudate nucleus.

White Matter Findings

White matter data point to unexpected findings which were not parallel with the gray matter results (See *Figure 9)*. White matter data revealed that for the stuttering group, increased volume of white matter in childhood years presented itself as significantly less white matter volume in adulthood. Overall, CWPS group and CWRS showed more areas of increased white matter volume than normally fluent children, while AWS group had significantly more areas of

reduced white matter volume than normally fluent adults. The regions where the recovered group and the persistent group had more white matter volume than normally fluent children included right inferior frontal gyrus, right middle temporal gyrus, right and left middle frontal gyrus, as well as cerebellum regions such as right cerebellar tonsil, right cerebellar declive, and right cerebellar pyramis. Both CWPS and CWRS showed less white matter volume than CWNS in precentral gyrus (left and right hemispheres, respectively). Compared to the persistent group, the recovered group showed more areas of increased white matter such as left cerebellum, right cerebellar tonsil, left inferior frontal gyrus, right inferior temporal gyrus, and right middle frontal gyrus.

All in all, the results of the current data suggest that compared to normally fluent children, children with persistent stuttering showed abnormal structure in cortical regions such as precentral gyrus, postcentral gyrus and subcortical regions such as caudate nucleus. Consistent with the discussion about the findings of AWS, these structural abnormalities that are located in the central areas or basal ganglia region may lead to disrupted communication between various regions of the brain involved in sensory and motor control of speech (Ludlow and Loucks, 2003).

CHAPTER V: DISCUSSION

Overview

Anatomical and functional brain differences between people who stutter and those who are normally fluent have been found in certain areas of the brain (Beal et al, 2007; Brown et al., 2005; Chang et al, 2008; Foundas et al., 2001, 2003; Jancke et al., 2004; Lu et al, 2010; Sommer et al., 2002; Watkins et al., 2008). The present study is a first attempt to investigate structural neural bases of stuttering in both children and adults who stutter. The imaging data for both children and adult population were collected with the same scanner and processed in an identical manner with the same threshold. This approach provides a basic way to understand developmental changes in stuttering. However, differences between the adult and child brains proved challenging to normalize, which still needs to be resolved in a future statistical comparison. Consequently, the current study took the first step in comparing groups of adults and groups of children separately followed by a descriptive comparison of the adult and child groups. In addition, the present study attempted to replicate the structural neuroimaging study in children study by Chang and colleagues (2008). The current study is the first VBM study to report voxel-based based morphometry (VBM) differences in white matter among children who stutter, children who have recovered from stuttering and normally fluent children.

The present data correspond to findings from several recent structural neuroimaging studies of adults and children who stutter. In parallel with the previous findings, widely distributed areas of gray and white matter volume increases and decreases were found in persons who stutter relative to normally fluent speakers (Beal et al., 2007; Chang et al., 2008; Lu et al., 2010). Particular regions of gray and white matter difference between AWS and normally fluent

controls include basal ganglia structures (i.e. putamen, caudate), thalamus, cerebellum structures, cingulate gyrus, as well as other speech-relevant motor and sensory regions in the frontal lobe, parietal and temporal regions. Particular regions of gray and white matter differences between children who stutter and fluent controls include inferior frontal gyrus, precentral gyrus, anterior cingulate, postcentral gyrus and other areas related to sensory and motor control of speech in frontal and temporal lobe regions. These regions have been documented as comprising a possible neural signature of stuttering by previous anatomical neuroimaging studies of adults and children (Beal et al., 2007; Chang et al., 2008; Jancke et al., 2004; Lu et al., 2010).

Gray Matter Differences between AWS and AWNS

The gray matter findings for the adult comparisons indicated that stuttering speakers had increased volume in particular subcortical structures such as the bilateral putamen and thalamus; and cortical structures including cingulate gyrus, postcentral gyrus, precentral gyrus, supramarginal gyrus, middle and superior frontal gyri.

Subcortical Differences

The largest clusters of increased gray matter in AWS were found in the bilateral putamen and thalamus. The basal ganglia is known to be involved in choosing, initiating and carrying out voluntary movements (Brown et al., 2005; Fabbro, Clarici & Bava, 1996; Pickett, Kuniholm, Protopapas, Friedman, Lieberman, 1998). Deviations in the anatomy and function of the basal ganglia structures (i.e., putamen, caudate nucleus, substantia nigra, or subthalamic nucleus) have been associated with the presence of stuttering in previous reports (Alm, 2004; Fox et al., 1996; Giraud et al., 2008; Lu et al., 2010; Wu et al., 1995). Specific differences in the putamen in AWS were reported in several functional neuroimaging studies (Braun et al., 1997; Fox et al.,

2000). Watkins et al. (2008) reported increased neural activity in the left putamen in people who stutter that was not related to the fluency of speech or the type of auditory feedback received. Chang et al. (2009) also found that compared to controls, AWS showed increased neural activation in bilateral putamen and precentral motor regions during speech and non-speech production. In a combined functional (fMRI and SEM) /anatomical (VBM) study, Lu et al. (2010) found heightened neural activation in the bilateral putamen accompanied by increased gray matter volume in left putamen of AWS compared to fluent controls. There have also been case reports of acquired stuttering showing the involvement of focal lesions of putamen in neurogenic stuttering (Ciabarra, Elkind, Roberts & Marshall, 2000; Soroker, Bar-Israel, Schechter, Solzi, 1990; Van Borsel, 2003). Ludlow & Loucks (2003) reported that putamen is the most frequently reported basal ganglia structure in case reports of acquired stuttering. Based on this evidence for alterations in the basal ganglia, Alm (2004) suggested that a basal ganglia-thalamocortical motor circuit running through the putamen to the supplementary motor area is involved in stuttering. Lu et al. (2010) also suggested that atypical anatomy compromises the basal ganglia-thalamocortical motor circuit of AWS.

Cortical Differences

AWS had increased cortical volume in the left posterior cingulate, right anterior cingulate, bilateral postcentral gyri, right precentral gyrus, left supramarginal gyrus, bilateral middle frontal gyrus and superior frontal gyrus on both hemispheres, which follows recent reports (Beal et al., 2007; Lu et al., 2010).

Anterior cingulate and posterior cingulate differences have been associated with stuttering in previous PET and fMRI studies (Braun et al., 1997; Brown et al., 2005; De Nil,

Kroll, Kapur, Houle, 2000; De Nil, Kroll, Lafaille, Houle, 2003). According to De Nil et al. (2003), increased activation in bilateral anterior cingulate of people who stutter might be indicative of heightened anticipatory reactions to stuttering. A similar pattern, where stuttering subjects showed increased activation in bilateral anterior cingulate gyrus, was also observed by Braun et al. (1997). De Nil et al. (2003) reported reduced activation in the left anterior cingulate in people who stutter following treatment.

Current results showed that in contrast to increased gray matter volume in postcentral gyrus in right hemisphere, AWS showed less gray matter volume in left postcentral gyrus. The difference in the postcentral gyrus may be relevant because it is involved in somatosensory and proprioceptive inputs to speech relevant oral structures (such as lip and tongue) as well as higher integration of these sensory modalities. The left supramarginal gyrus difference is important because this structure is involved in phonological processing of words, and integration of auditory and somatosensory inputs for speech production (Celsis et al., 1999; Damasio & Damasio, 1980; Guenther, 2001). Differences in anatomy and functioning of these parietal lobe structures in people who stutter have been reported previously (Kell, et al., 2009; Lu et al., 2010; Watkins et al., 2008).

Numerous frontal lobe anatomical differences have been reported in previous findings. Present data showed increased gray matter volume in bilateral superior frontal and middle frontal gyri, as well as right precentral gyri in AWS. Precentral gyrus has been well-documented as an important structure where the motor representations of articulators are located (Pulvermuller et al., 2006). In contrast to the increase in gray matter volume in right precentral gyrus in the current study, Lu et al. (2010) and Beal et al. (2007) reported increased gray matter volume in left precentral gyrus in AWS. Although the developmental mechanism behind this structural

change is still unclear, Chang et al. (2008) also found increased gray matter volume in right precentral gyrus in persistent stuttering children compared to recovered children group. These atypical anatomical findings may be related to functional studies in which heightened activation levels were detected in the right precentral gyrus, as well as right superior and middle frontal regions during a reading task in people who stutter as opposed to fluent controls (De Nil et al., 2003; Lu et al., 2010; Preibisch et al., 2003).

AWS showed decreased gray matter volume in parietal lobe regions such as bilateral superior parietal lobule, right inferior parietal lobule, and bilateral precuneus. While specific roles of these structures in speech production are unclear, functional and structural differences in AWS have been previously reported in the literature (Lu et al., 2010; Ingham, Fox, Ingham & Zamarripa, 2000; Watkins et al., 2008).

Cerebellum Differences

Multiple reports have implicated aberrant function in right and left cerebellum structures in AWS (Brown et al., 2005; Fox et al., 1996; Howell, 2004; Lu et al., 2010). The present data suggested that cerebellar functional differences in AWS could be related to reduced gray matter volume in the left cerebellum. The cerebellum has been associated with motor control of speech articulators, timing and coordination of speech gestures, and temporal organization of internal speech (Ackermann, 2008). Recently, Lu et al. (2010) reported that AWS showed higher activation in right cerebellum but less gray matter volume in the same region. Beal et al. (2007) reported that AWS showed increased gray matter volume in right cerebellum. Chang et al. (2008) also found decreased gray matter in the left cerebellum of children who stutter compared

to recovered children. Taken together, it is possible that overactivation in the right cerebellum of AWS might compensate for reduced gray matter volume on the left side.

White Matter Differences in Adults

Our white matter results showed that adults who stutter tended to have significantly more volume only in left anterior cingulate gyrus compared to adults who are normally fluent. In contrast, AWS exhibited decreased white matter in numerous cortical and cerebellar areas. The areas included white matter proximal to left superior temporal gyrus, bilateral middle temporal gyrus, bilateral precentral gyrus, right postcentral gyrus, right supramarginal gyrus, left cerebellar pyramis, left posterior cerebellar tuber, and bilateral posterior cerebellar tonsil. Some of these white matter areas likely connect speech production regions while others have questionable connections to speech production regions. Some of the previous structural neuroimaging studies have not reported decreased white matter volume in these brain regions of adults who stutter (Beal et al., 2007; Foundas et al., 2001; Jancke et al., 2004), while other studies support some of the current findings (Lu et al., 2010; Sommer et al., 2002; Watkins et al., 2008). Lu et al. (2010) reported reduced white matter volume in right precentral gyrus, left superior temporal gyrus right cerebellar tonsil, right cerebellar pyramis, and left cerebellar tuber of people who stutter. Other studies used DTI method to analyze white matter integrity or connectivity. Although the connection between white matter FA values and volume has not been documented in the literature, the increased FA might be related to increased white matter volume as increased FA levels imply a higher degree of myelination. Parallel with the current findings, Sommer et al. (2002) reported lower fractional anisotropy (FA) in adults who stutter than normally fluent adults in left rolandic operculum above the Sylvian fissure. Watkins et al. (2008) also found that people who stutter had lower FA values than normally fluent participants in white

matter areas underlying bilateral precentral gyrus, right supramarginal gyrus, bilateral posterior cerebellar lobes, and right anterior cerebellar lobe. On the other hand, in contrast with the findings of the current study, some VBM studies reported increased white matter volume in right hemisphere regions of AWS (Beal et al. 2007; Jancke et al., 2004).

Disrupted connection between subcortical and cortical structures

Taking the gray matter and white matter differences together, the current results indicate a neural signature for persistent stuttering in adults might be aberrant white matter connections that connect subcortical (basal ganglia, thalamus) and cortical structures (frontal, temporo-parietal). This inference is related to the postulate of a deviant basal ganglia-thalamo-cortical-circuit (BGTC) discussed in Lu et al. (2010) study and the EXPLAN theory predictions discussed in Watkins et al. (2008) study. EXPLAN theory assumes that motor processes (EX) and language (PLAN) are critical in fluent speech control (Howell, 2010). Therefore, connections among structures involved in motor control, articulatory planning, sensory feedback are critical for fluent speech. Disrupted connections accompanying deviant subcortical and cortical anatomy could explain altered neural activation patterns in subcortical and cortical motor and sensory structures.

The basal ganglia-thalamo-cortical motor circuits that pass through the putamen have been proposed to play an important role in stuttering (Alm, 2004). The thalamus receives sensory input from almost all parts of the body and it is a final relay station for sensory information being transmitted to the cortical structures. Sensory-motor information from the cerebral cortex enters the basal ganglia from the putamen, which transmits important timing and sequencing signals for minute to minute modulation of speech relevant brain structures. In addition, the thalamus

receives continuous timing and sequencing from the cerebellum. Therefore, it becomes clear that if a sensory-motor circuit for speech production that passes through the putamen, thalamus, and cerebellum is compromised by insufficient white matter connectivity, neural coordination of speech could be subject to disruption. Disruption of transmission of information to and from the putamen could lead to stuttering-like disfluencies. For instance, if the timing cue is disrupted, then the speakers might repeat the first sound of word 'fuh- fuh- friend', prolong it as in 'fffffriend' or pause after producing the first sound 'f-riend' (Howell, 2010). In line with this idea, Fox et al. (1996) reported hyperactivity of the cerebellum, thalamus, and basal ganglia structures in people who stutter during a reading task compared to fluent controls.

Our data suggest AWS have decreased white matter volume underlying the sensory-motor structures of this loop (precentral gyrus, postcentral gyrus, superior temporal gyrus, supramarginal gyrus and putamen. This reduction in white matter fiber coherence projecting from cortical structures might result in compensatory 'overactivation' of putamen and the cortical structures involved. On the other hand, the increase in gray matter volume in these areas could be due to this 'overactivation' pattern as it has been well documented in the literature that practice or training over an extended period of time can lead to an increase in gray matter volume (Gaser & Schlaug, 2003; Ilg et al., 2008). Therefore, increased gray matter volume in bilateral putamen, as well as in cortical regions such as bilateral superior frontal gyrus, bilateral medial frontal gyrus, right precentral gyrus, bilateral postcentral gyrus could be conceived as compensation for disrupted connectivity between cortical and subcortical regions due to reduced white matter volume. This explanation is also parallel with the previous functional neuroimaging findings which indicated overactivation in putamen of adults who stutter (Chang, Kenney, Loucks & Ludlow, 2009; Lu et al., 2010; Watkins et al., 2008) as this evidence supports the

results of the current study where increased gray matter volume putamen could be due to 'overactivation' to compensate for reduced white matter volume.

Similarly, the current data showed reduced gray and white matter volume in the cerebellum of adults who stutter compared to normally fluent adults. This suggests that information or transmission of information important for minute to minute motor control for speech from the cerebellum to the thalamus could be disrupted. This could also be related to increased gray matter volume observed in the bilateral thalamus of adults who stutter since overactivation of the thalamus as a compensatory mechanism for disrupted signal transmission from the cerebellum used over a lifetime of stuttering is a factor that might lead to increased gray matter volume in these structures of adults with persistent stuttering (Gaser & Schlaug, 2003; Ilg et al., 2008).

Ludlow and Loucks (2003) proposed that stuttering is likely caused by a dysfunction in cortical structures such as postcentral sensory areas, premotor and motor areas or subcortical structures such as corpus callosum, basal ganglia (i.e. putamen and caudate), thalamus because these structures have connections to a wide range of areas of the brain. They suggested that dysfunction in these regions of the brain may interfere with the rapid and precise timing requirements of accurate speech production. Our VBM evidence pointing to widespread anatomical differences in the present study is consistent with this proposal by Ludlow and Loucks (2003).

Replication Results (Chang et al., 2008)

The present study offered an opportunity to replicate the gray matter results of Chang et al. (2008). In this section, we will discuss whether we were able to reproduce the results reported

by Chang et al. (2008). We will then relate our results to selected studies of AWS to evaluate how childhood neuroananatomical correlates of stuttering differ from that of adults. Recovery from stuttering is treated as a specific section.

The same children subjects were used in the current study, but Chang and colleagues used a pediatric template for spatial normalization of images in contrast to the adult template used in the current study. The Gaussian smoothing kernel size used in the current study was 8 mm as opposed to 12 mm in Chang et al. (2008) study. It is possible that the smoothing kernel in Chang et al. (2008) study was too large to detect the structural differences that we identified in the current study. Also our analyses were conducted using SPM 5 software, while Chang et al. used the tools of FSL program. In our statistical parametric maps, a voxel cluster threshold size of >30 was applied to all the resultant statistical parametric maps (SPMs) at a p value of 0.005 (uncorrected) as opposed to $p < 0.001$ (uncorrected) used by Chang et al. (2008). Chang et al. (2008) did not report a comparison of white matter volume using VBM and this has been completed in this study. Instead our white matter volume results will be compared to Chang et al.'s DTI findings.

Differences between CWS and CWNS

Cortical Differences

The findings of the current study are similar to the results of Chang et al. (2008) study in that CWPS group had less gray matter volume than controls in sensory-motor cortical areas such as left precentral gyrus, left superior frontal gyrus, left paracentral lobule and bilateral medial frontal gyrus. In terms of differences, our findings showed that CWPS had more gray matter than their normally fluent peers in left inferior frontal gyrus, and left postcentral gyrus. On the other

hand, Chang et al. (2008) reported less gray matter volume in left inferior frontal gyrus in children who stutter than fluent controls. Our analysis of CWPS showed decreased gray matter volume in left caudate nucleus compared to controls but was not reported by Chang et al. (2008).

Considering white matter patterns, our analysis of CWPS showed less white matter volume than normally fluent children in important areas for speech sensory and motor control such as left precentral gyrus, right superior parietal lobule, and right middle frontal gyrus. This may relate to Chang et al. (2008) DTI findings of reduced FA levels in white matter tracts including superior longitudinal tract, arcuate fasciculus, corticospinal/posterior thalamic radiation in stuttering group compared to controls.

The children with persistent stuttering group had more white matter volume than control group in regions including right middle temporal gyrus, right superior frontal gyrus, right posterior cerebellar declive, right inferior frontal gyrus, bilateral precuneus, and left cuneus. Chang et al. (2008) reported higher FA values in two white matter tracts, right uncinate fasciculus and right inferior longitudinal fasciculus of children who stutter compared to fluent controls. Certain white matter areas in our analysis could involve these tracts so perhaps the increased FA in our subjects is related to increased white matter volume.

Overall, even though there were many similarities, our results did not fully replicate the findings of Chang et al. (2008) study, which might be due to the methodological differences between the two studies (i.e. different normalization templates, software to analyze). However, this implies that further studies with a larger pediatric sample are needed to confirm the results of Chang et al. (2008) study and the current study.

Differences in CWRS versus CWPS and CWNS

Gray matter differences

Children who recovered from stuttering showed significantly more gray matter than children with persistent stuttering and children who are normally fluent across a wide range of regions including right and left middle temporal gyrus, bilateral cerebellar declive, bilateral medial frontal gyrus, bilateral superior frontal gyrus, left anterior cingulate, and right inferior frontal gyrus. On the other hand, the recovered group showed less gray matter than persistent group in only left cingulate gyrus, and they had less gray matter than the control group only in left medial frontal gyrus and right cingulate gyrus. Interestingly, gray matter volume in left and right cingulate gyrus was consistently reduced in the recovered group as opposed to persistent and control groups. However, the findings regarding cingulate gyrus were not consistent with Chang et al. (2008), as they found that recovered group had more gray matter in cingulate gyrus than children with persistent stuttering. Reduced gray matter volume in the cingulate gyrus of children who recovered from stuttering may be explained by neuroplasticity. Reduction in gray matter volume in cingulate gyrus could be due to pruning of dendrites in this region to allow for organization of new networks of dendrites.

Another interesting finding in the results of the current study was that the areas where the persistent stuttering group had less gray matter volume than controls, such as in superior frontal gyrus and medial frontal gyrus, were significantly increased in the recovered group compared to persistent group and fluent controls. Although Chang et al. (2008) also reported gray matter volume differences in all of these regions, some of the results are inconsistent with their findings. They reported that compared to the recovered and persistent groups, normally fluent controls had

significantly more gray matter in almost all of these regions and they found no areas of gray matter where fluent controls had less gray matter than the stuttering group. In addition Chang et al. (2008) reported decreased gray matter volume in bilateral cerebellar declive in recovered children compared to persistent group while the results of the current study showed increased gray matter in these areas in recovered group compared to both persistent and control groups. The failure to replicate the results of Chang et al. (2008) study might be due to use of different templates to normalize images, and other differences in methods of these two studies. However, given that the prediatric sample in the current study is the same as in Chang et al. (2008) study, the limitations of the use of VBM method with this age group should also be acknowledged.

Increase in cerebellum gray matter volume (as well as white matter volume, to be discussed in the next section) could be another marker for recovery from persistent stuttering. As discussed previously, the cerebellum is well documented to be a crucial structure for motor control of speech articulators, timing and coordination of speech gestures, and temporal organization of internal speech (Ackermann, 2008). The results of the current study exhibited that children with persistent stuttering showed significantly less gray matter volume in cerebellar regions than recovered children. Similarly, AWS also had significantly less gray matter volume in cerebellum than normally fluent controls. Increase in cell size or neural or glial cell genesis in cerebellum could be a crucial marker for natural recovery from developmental stuttering. The gray and white matter results of recovered children group in the current study are consistent with such an idea.

White Matter Differences

Current results of changes in white matter volume in children who recovered from stuttering were very similar to the gray matter findings. Children who recovered from stuttering showed significantly more areas of increased white matter volume than both the persistent group and normally fluent controls such as right medial frontal gyrus, right and left superior frontal gyrus, right superior temporal gyrus, right inferior temporal gyrus, as well as cerebellum regions (right posterior cerebellar pyramis, right posterior cerebellar tonsil, and left cerebellum). The only regions where recovered group showed less white matter volume than the persistent group and control group were right precentral gyrus and cerebellum regions such as right posterior cerebellar declive, left posterior cerebellar tonsil, right cerebellar tuber, and left cerebellar uvula.

The current results, which showed that compared to control and persistent groups, recovered group showed more white matter volume, are not consistent with the results of Chang et al. (2008) study. Chang et al. (2008) found that the control group had higher FA values than the combined recovered and persistent groups. On the other hand, parallel with the findings of the current study, Chang et al. (2008) also reported that recovered group had higher FA values than persistent group in white matter tracts such as right superior longitudinal fasciculus.

In terms of white matter volume, children who recovered from stuttering showed both more and less volume in several cerebellar regions. Mechanisms that might explain reduced white matter volume is pruning of neurons. Mechanisms that could increase white matter volume are increased and extensive dendritic arborization of gray matter. These ideas cannot be verified with in-vivo imaging but these are basic mechanisms that account for brain tissue changes in animal models.

Explaining stuttering persistence and recovery in the light of contemporary theories or models of stuttering

The current literature in stuttering lacks a comprehensive, yet simple, theory or model which can explain the complex nature of stuttering. Contemporary theories or models of stuttering fail to account for all aspects of stuttering including biological, behavioral and psychological factors that can lead to stuttering. Here I will discuss the findings of the current study in the light of the DIVA model (Directions into velocities of articulators), which is one of the major contemporary models of speech production, which has considerable relevance for understanding stuttering (Civier, Tasko & Guenther 2010; Max, Guenther, Gracco, Ghosh & Wallace, 2004). Our current neuroanatomical data can potentially inform the stuttering simulation currently modeled by DIVA.

The DIVA model is a neural network model proposed by Guenther and his colleagues to explain motor, somatosensory, and auditory processes involved in the acquisition and control of speech movements (Guenther, 2006; Guenther, Ghosh & Tourville, 2006). According to Guenther (2006), the speech production process starts by activating a "speech sound map" cell located in the frontal operculum, followed by the transmission of motor commands to motor cortex via a feedforward control system and a feedback control system (See *Figure 10*). The feedback control system is further divided into auditory target region and somatosensory target region.

Feedback control system

According to DIVA model, the left frontal operculum, which hosts speech sound map cells, has axonal projections to auditory cortical areas where the auditory target region for the

speech sounds that are being produced is located. Guenther (2006) did not specify which cortical areas house the auditory target region. As a person is producing speech, their speech is compared to the target via the auditory feedback from the periphery. Upon receiving auditory information that is outside the target region, the "auditory error cells" in the superior temporal gyrus and planum temporale are activated in order to send "corrective motor commands" to the motor cortex. The Chang et al. (2008) finding that CWS had more gray matter volume than normally fluent controls in superior temporal gyrus and planum temporale may indicate these corrective regions follow a different developmental course in CWS that could suggest atypical function. Replication did not find significantly increased gray matter volume in superior temporal gyrus and planum temporale of either AWS or CWS compared to normally fluent controls. Instead, our analysis indicated AWS had less white matter volume in the bilateral superior temporal gyrus, which following the DIVA model logic, might disrupt connections with the auditory error map area or disrupt the transmission of corrective motor commands from superior temporal gyrus to the motor cortex. Because the replication did not find differences in gray or white matter volume in these auditory corrective regions in children, it is possible that dysfunction of these region in stuttering arises after the school age period.

According to DIVA model, somatosensory feedback control system also operates along with the auditory feedback control system. In this model, "somatosensory state maps", which correspond to the representation of tactile and proprioceptive information, are located in the postcentral gyrus and supramarginal gyrus, while the "somatosensory error map" is located in the supramarginal gyrus. When the tactile or proprioceptive cues from speech structures are outside the somatosensory target region, the cells in this map are activated. The results of the current data suggest differences in somatosensory regions. The AWS and CWPS had significantly

increased gray matter volume in the postcentral gyrus compared to normally fluent controls, which could signal a tendency towards aberrant activation of the somatosensory map cells in this region. In addition, we found that the ever-stuttered group had significantly less gray matter volume than CWNS group in left supramarginal gyrus, which may suggest that there are fewer "somatosensory error map cells" in that region, and this may result in a breakdown in the somatosensory feedback transmission to the motor cortex. While a breakdown at the somatosensory feedback control level of the DIVA model may be a marker for stuttering persistence, it fails to explain the mechanisms behind recovery because the results of the current study indicated no difference in gray or white matter volume in these areas between recovered children and children with persistent stuttering.

Feedforward Control System

According to the DIVA model, feedforward motor commands area correspond to projections from premotor cortex (left frontal operculum), and cerebellum to primary motor cortex. The cerebellum is well-known to be involved in motor control of speech articulators, timing and coordination of speech gestures, and temporal organization of internal speech (Ackermann, 2008). And according to Middleton and Strick (2001), cerebellum receives input from auditory and somatosensory areas and has strong feedforward connections with the primary and premotor cortices. Therefore, as discussed previously, dysfunction of the cerebellum might lead disruptions of feedforward commands and subsequently stuttered speech. The data from the current study found that AWS had significantly less gray matter volume than AWNS in left cerebellum. In addition, CWPS had more white matter volume than control group in right cerebellum. Recovered group showed significantly more and less white matter volume than the persistent group in various cerebellar regions. These results support the idea that dysfunction of

the cerebellum in the feedforward control system in DIVA model might be a marker of stuttering, but the developmental trajectory remains unclear.

As emphasized previously, the results of the current study showed large clusters of increased gray matter in bilateral putamen, bilateral thalamus, and sensory-motor cortical areas of AWS compared to normally fluent controls. But CWPS showed less gray matter volume than normally fluent children in left caudate nucleus and some cortical regions involved in sensory and motor control for speech production. Recently, a new formulation of the DIVA model, called GODIVA (Gradient Order DIVA) has been proposed (Civier et al., 2010). According to GODIVA model, the integrity of the basal ganglia - thalamus - left ventral premotor cortex loop is crucial for properly conducting feedforward commands for speech production. Civier et al. (2010) proposed that this circuit may be disrupted by aberrant neural structure and function due to white matter impairment in the corticostriatal projections involved in transmission of motor commands to the muscles or due to increased dopamine in the striatum causing a ceiling effect in the thalamus. We found reduced white matter volume in this circuit in AWS relative to fluent controls, which supports the first hypothesis of the GODIVA model. The second hypothesis could explain increased gray matter volume in bilateral thalamus of AWS.

Overall, the results of the current study are consistent with the idea that stuttering might be caused by a breakdown at single or multiple levels in the DIVA model. This may potentially explain different phenomena of stuttering. For instance if a person's stuttering is caused by a breakdown in the auditory control feedback subsystem, then treatment could be developed to address this. Such an idea may also explain why delayed or altered auditory feedback leads to fluent speech in some people who stutter but not all. It is likely that a person who has dysfunction at multiple levels in this model might have more severe stuttering than another

person who has a breakdown at a single level in this system. However, caution is needed that these are all speculations and empirical evidence is necessary to test the validity of the DIVA model in larger groups of adults and children who stutter. In addition, future research needs to differentiate the mechanism that leads to stuttering from other speech disorders such as dysarthria, which might as well be explained by a breakdown at a level in the DIVA model.

Limitations of the current study and future directions

A major limitation of the current study is that despite using the same dataset, we did not replicate the results of Chang et al. (2008) study fully. Even though we could replicate some of the results, opposite findings also frequently occurred. These differences might be attributed to differences in methodology of these two studies, and specifically differences in the preprocessing (i.e. normalization using different brain templates, different kernel size for smoothing) of these images for analysis. Yet, these limitations of VBM should be acknowledged and future studies using a larger pediatric sample are needed to confirm the results of which study are more valid. Certain limitations that are similar to the Chang et al. (2008) study should be acknowledged. Children in this study were between 9 and 12 years of age, and this age range is several years past the stuttering onset. Therefore, it is difficult to make a statement whether the structural differences in stuttering children group are due to compensatory behaviors associated with stuttering or not. However, studying the neuroanatomy of pediatric brains is challenging because the brains of younger children (6 years of age of younger) are too variable in size and shape to be compared directly (Muzik et al., 2000; Burgund et al., 2002). The small size for the pediatric group is also a limitation since it impacts the statistical power of the pairwise comparisons in VBM. Structural studies need to be conducted with a larger children and adult sample. The VBM method also has some limitations. For example, if the volume differences are subtle or if they are

located in small brain regions, which might be affected by imaging artifacts, VBM might fail to identify these differences. VBM also does not provide information about connections between white matter regions. Therefore, future structural studies will need to employ other methods such as DTI to understand white matter changes and white matter connections in adult and children groups. Current study was designed to assess structural differences in adults and children who stutter relative to fluent controls. Therefore we are limited in proposing claims about function, and functional studies need to confirm speculations regarding functional aspects of the structures discussed in children and adult groups.

Clinical implications of the current study

The results of the current study can help clinicians understand that neuroanatomical differences in children and adults who stutter could be involved in stuttering. This study alone is not sufficient to make statements about prediction of onset of developmental stuttering, or therapy techniques for the treatment of stuttering. However, if further functional and structural studies confirm current results, clinicians can gain a better understanding in predicting onset of stuttering, and identification of 'at-risk' children. In addition, they may develop individualized treatment for people who stutter or defer to alternative intervention techniques such as pharmaceuticals to assist in the functioning of structures in basal ganglia-thalamocortical circuitry, or biofeedback for children with disrupted connectivity between sensory and motor structures involved in speech production.

Conclusions

The purpose of the current project was to identify neurological differences associated with the presence of stuttering that could explain a range of factors related to causation,

development, persistence, and recovery. Using the VBM method, the present study demonstrated significant gray and white matter volume differences in brain areas important for speech production in adults who stutter, children with persistent stuttering, and recovered children relative to controls. These areas included subcortical structures, cortical areas, as well as cerebellar regions. Taken together the results of adult group and pediatric group, we proposed that developmental stuttering could be related to aberrant gray and white matter volumes in a widely distributed neural network which may lead to disrupted transmission of sensory or motor information among speech relevant areas in this neural circuitry. In addition, aberrant development pattern in these areas may present risk for the onset of stuttering. Further functional and structural studies are needed to confirm and sort out the effect of different analytical approaches for understanding brain development in stuttering.

CHAPTER VI: TABLES

Tables 1-11

Table 1: *Structural Neuroimaging studies of stuttering*

Study	**Subjects**	**Tissue Type**	**Method**	**Direction of change**	**Region**
Foundas et al. (2001)	16 AWS 16 Controls	GM	Manual Tracing-ROI Volume of tissue in ROI	AWS> Controls AWS -Reduced magnitude of the planar asymmetry AWS- more gyral variants	AWS> in Bilateral Planum temporale (PT), prefrontal cortex, L occipital lobe AWS -anomalous anatomy in perisylvian speech and language areas
Sommer, et al. (2002)	15 AWS, 15 controls	WM	DTI: Variable: Fractional anisotropy (FA)	AWS<Controls – Reduced FA	FA in AWS< Controls in LH Rolandic Operculum (RO) near PMA and inferior arcuate fasciculus linking temporal and frontal areas
Jancke et al. (2004)	10 AWS; 10 Controls	WM GM (no difference)	VBM Variable: tissue volume	AWS> Controls within four clusters on the RH Controls> AWS in auditory cortex LH	AWS> in RH STG including planum temporale (PT); RH PrCG, IFG comprising pars opercularis; MFG Controls> in LH Heschl's gyrus, PT
Beal et al. (2007)	26 AWS; 28 Controls	GM WM	VBM Tissue volume	AWS>Controls in 5 significant GM clusters AWS>Controls in 3 significant WM clusters	GM: 1) RH STG 2) RH Cerebellum 3) LH STG 4) LH IFG 5) LH STG WM: 1) RH Insula 2) RH IFG 3) LH MTG
Chang et al. (2008)	8 CWS (persistent), 7 Recovered, 7 Controls	GM WM	VBM Tissue Volume DTI FA	Controls >Persistent & Recovered GMV Controls >Persistent & Recovered: reduced FA in left WM tracts.	**GM**: 1) bilateral IFG 2) left anterior CG 3) bilateral SMA 4) left SMG 5) right temporal regions **WM:** 1) Reduced WM tracts in left RO for PDS and recovered group
Lu et al. (2010)	12 AWS, !2 Controls	GM WM	VBM Tissue volume	Controls> AWS AWS> Controls	Controls> GM in Left MFG, ASTG; WM underlying L PSTG AWS> GM in L Putamen

Table 2

List of Gray Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Adults Who Stutter (S) and Adults Who Do Not Stutter (NS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
S>NS	Subcortical Regions	Putamen	Left	2263	4.57	-18, -2, 10
		Putamen,	Right	2134	4.32	30, -8, 4
		Thalamus	Left	223	3.34	-20, -32, 0
		Thalamus	Right	116	3.15	20, -30, 0
	Cortical Regions Frontal	Superior Frontal Gyrus	Left	288	4.23	-20, 14, 40
		Middle Frontal Gyrus	Right	102	3.90	38, 40, 22
		Superior Frontal Gyrus	Right	55	3.70	10, 44, 42
		Superior Frontal Gyrus	Right	43	3.58	20, 56, 18
		Medial Frontal Gyrus	Left	165	3.49	-12, -28, 56
		Middle Frontal Gyrus	Right	160	3.42	28, 28, 38
		Superior Frontal Gyrus	Left	49	3.33	-10, 6, 62
		Precentral Gyrus	Right	89	3.12	16, -20, 58
		Anterior Cingulate	Right	31	3.07	12, 34, 24
		Superior Frontal Gyrus	Left	48	3.01	-8, 20, 56
		Medial Frontal Gyrus	Left	30	2.84	-8, 40, 38
	Cortical Regions Temporal-Parietal	Precuneus	Right	46	3.65	22, -56, 50
		Inferior Parietal Lobule	Right	136	3.61	48, -36, 44
		Postcentral Gyrus	Left	58	3.26	-58, -12, 24
		Posterior Cingulate	Left	194	3.11	-10, -50, 8
		Supramarginal Gyrus	Left	36	3.09	-46, -44, 36
		Postcentral Gyrus	Right	31	3.01	54,-18, 24
NS>S	Cortical Regions Temporal-Parietal	Superior Parietal Lobule	Left	299	4.00	-24, -64, 64
		Postcentral Gyrus	Left	51	3.38	-32, -42, 68
		Precuneus	Right	59	3.14	8, -76 ,48
		Inferior Parietal Lobule	Right	39	3.13	52, -38, 58
		Superior Parietal Lobule	Right	34	3.11	36, -66, 58
		Precuneus	Left	31	2.91	-12, -88, 42
		Superior Parietal Lobule	Left	41	2.90	-46, -62, 54
		Inferior Temporal Gyrus	Right	46	2.84	58, -6, -36
	Cerebellar Regions	Cerebellum	Left	114	3.11	-2 ,-86, -28

Table 3

List of White Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Adults Who Stutter (S) and Adults Who Do Not Stutter (NS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
S>NS	Cortical Regions Frontal	Anterior Cingulate	Left	49	3.11	-2, 30, 2
NS>S	Cortical Regions Frontal	Precentral Gyrus	Left	128	3.66	-26, -12, 66
	Cortical Regions Parietal-Temporal	Middle Temporal Gyrus	Left	505	4.22	-70, -32, -6
		Superior Parietal Lobule	Right	825	3.93	36, -66, 56
		Inferior Temporal	Right	153	3.88	62, -42, -18
		Postcentral Gyrus	Right	218	3.62	2, -46, 64
		Middle Temporal Gyrus	Right	160	3.55	68, -28, -10
		Superior Temporal	Left	73	3.48	-60, 6, 0
		Precuneus	Right	77	3.36	32 -82 40
		Inferior Parietal Lobule	Right	91	3.33	52 -38 54
		Supramarginal Gyrus	Right	41	3.27	58, -54, 36
		Middle Temporal Gyrus	Right	38	3.23	52, 10, -26
		Precentral Gyrus	Right	115	3.20	68, -4, 26
		Superior Temporal	Right	99	3.17	34, 6, -42
		Parahippocampal G.	Left	36	2.83	-28, -50, 10
		Middle Temporal Gyrus	Left	88	3.14	-68, -58, 4
		Superior Temporal	Left	134	3.04	-30, 4, -46
		Postcentral Gyrus	Right	69	2.93	60, -26, 48
	Cortical Regions Occipital	Middle Occipital Gyrus	Left	57	3.07	-56, -74, 10
		Middle Occipital Gyrus	Right	63	3.06	8, -96, 16
		Cuneus (Occipital L)	Left	90	3.05	-14, -88, 40
	Cerebellar Regions	Posterior Cerebellar Pyramis	Left	2873	3.84	-10 -80 -30
		Posterior Cerebellar Tuber	Left	46	3.09	-46 -90 -18
		Cerebellar Tonsil	Right	195	2.92	38, -42, -46
		Cerebellar Tonsil	Left	115	2.89	-46 -42 -42

Table 4

List of Gray Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Ever Stuttered Children (S) and Normally Fluent Children (NS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
S>NS	Cortical Regions Temporal	Parahippocampal Gyrus	Right	88	3.21	28, -24, -28
NS>S	Cortical Regions Frontal	Middle Frontal Gyrus	Left	72	3.24	-28, 26, 26
		Superior Frontal Gyrus	Right	31	3.08	18, 16, 58
		Cingulate Gyrus	Right	33	3.78	24, -14, 40
		Medial Frontal Gyrus	Right	60	3.57	16, 52, 6
		Superior Frontal Gyrus	Left	69	3.57	-16, 46, -12
	Cortical Regions Parietal	Supramarginal Gyrus	Left	107	3.50	-44 -40 30

Table 5

List of White Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Ever Stuttered Children (S) and Normally Fluent Children (NS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
NS>S	Cortical Regions Frontal	Middle Frontal Gyrus	Right	65	4.77	42, 16, 42
	Cortical Regions Parietal-Temporal	Inferior Temporal Gyrus	Right	177	3.44	64, -34, -26
		Postcentral Gyrus	Right	35	2.98	52, -12, 50
S>NS	Cortical Regions Parietal-Occipital	Inferior Parietal Lobule	Left	72	3.83	-40, -62, 44
		Cuneus	Left	92	3.61	0, -88, 8
		Precuneus	Right	51	3.56	2, -66, 42
		Inferior Semi-Lunar L	Left	32	3.40	-8 ,-60, -46
		Parahippocampal Gyrus	Left	36	3.34	-16, -50, 4
	Cerebellar Regions	Cerebellar Uvula	Right	54	2.87	18, -68, -32

Table 6

List of Gray Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Children with Persistent Stuttering (S) and Normally Fluent Children (NS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
S>NS	Cortical Regions Parietal-Occipital	Precuneus	Right	42	3.36	18, -70, 42
		Middle Occipital Gyrus	Left	72	3.13	-40, -68, 0
		Postcentral Gyrus	Left	47	3.38	-46, -26, 48
		Precuneus	Right	34	2.85	2, -82, 42
	Cortical Regions Frontal	Inferior Frontal Gyrus	Left	46	3.44	-40, 4, 26
		Orbital Gyrus	Right	54	3.06	22, 26, -26
NS>S	Cortical Regions Frontal	Medial Frontal Gyrus	Right	99	4.13	14, 52, 2
		Superior Frontal Gyrus	Left	80	3.79	-14, 46, -14
		Superior Frontal Gyrus	Left	109	3.71	-14, 28, 46
		Precentral Gyrus	Left	53	3.59	-12, -18, 68
		Medial Frontal Gyrus	Left	82	3.59	-12, 52, 14
		Medial Frontal Gyrus	Right	30	3.40	14, 34, 28
		Middle Frontal Gyrus	Right	53	3.33	32, 24, 26
		Medial Frontal Gyrus	Right	34	3.29	12, 24, 40
		Middle Frontal Gyrus	Left	54	3.21	-30, 32, 22
		Medial Frontal Gyrus	Left	55	3.14	-14, 30, 30
	Cortical Regions Parietal	Inferior Parietal Lobule	Right	54	3.68	46, -28, 28
		Paracentral Lobule	Left	44	3.12	-14, -32, 52
	Subcortical Regions	Caudate	Left	94	3.01	-8, 18, 14

Table 7

List of White Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Children with Persistent Stuttering (S) and Normally Fluent Children (NS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
S>NS	Cortical Frontal Regions	Superior Frontal Gyrus	Right	125	4.29	6, 68, 20
		Inferior Frontal Gyrus	Right	50	3.54	24, 26, -24
		Middle Frontal Gyrus	Right	42	3.09	52, 36, 16
	Cerebellar Regions	Posterior Cerebellar Declive	Right	63	3.61	46, -56, -18
	Cortical Parietal-Temporal Regions	Inferior Parietal Lobule	Left	70	4.24	-40, -62, 44
		Middle Temporal Gyrus	Right	92	3.84	50, -74, 16
		Parahippocampal Gyrus	Left	43	3.50	-14, -50, 4
		Inferior Parietal Lobule	Left	41	3.37	-48, -40, 28
		Precuneus	Left	45	3.36	0, -56, 36
		Precuneus	Right	37	3.31	2, -66, 20
		Precuneus	Right	51	3.17	10, -50, 30
		Precuneus	Left	44	3.12	-12, -50, 32
	Occipital Regions	Cuneus	Left	136	4.00	0, -88, 8
NS>S	Cortical Frontal Regions	Middle Frontal Gyrus	Right	52	4.39	40, 14, 44
		Precentral Gyrus	Left	85	3.76	-32, 0, 32
	Cortical Regions Parietal-Occipital	Superior Parietal Lobule	Right	45	4.67	34, -60, 54
		Middle Occipital Gyrus	Right	55	3.89	48, -54, -6
		Inferior Occipital Gyrus	Left	48	3.69	-34 -92 -12

Table 8

List of Gray Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Children who Recovered from Stuttering (R) and Children with Persistent Stuttering (PS) On a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
PS>R	Subcortical Regions	Cingulate Gyrus	Left	31	2.83	-20, -22, 34
R>PS	Cortical Regions Frontal	Medial Frontal Gyrus	Left	168	4.63	-12 , 34, 30
		Medial Frontal Gyrus	Left	78	4.58	-8, -22, 52
		Medial Frontal Gyrus	Right	322	4.29	14, 34, 26
		Superior Frontal Gyrus	Right	2645	4.11	12, 30, 48
		Middle Frontal Gyrus	Left	111	3.93	-30, -2, 46
		Superior Frontal Gyrus	Left	39	3.73	-38, 18, 46
		Superior Frontal Gyrus	Left	85	3.69	-14, 62, -16
		Anterior Cingulate	Left	66	3.61	-8, 22, 18
		Inferior Frontal Gyrus	Right	139	3.53	20, 20, -16
		Superior Frontal Gyrus	Left	53	3.35	-14, 6, 62
		Superior Frontal Gyrus	Right	246	3.21	8, 70, 0
		Inferior Frontal Gyrus	Right	31	3.11	38, 26, -12
	Cortical Regions Occipital-Temporal	Fusiform Gyrus	Right	2256	4.79	42, -78, -14
		Middle Temporal Gyrus	Right	308	3.94	70, -54, 2
	Cerebellar Regions	Middle Temporal Gyrus	Right	70	3.55	44, 2, -24
		Uncus	Left	79	3.08	-40 -14 -30
		Middle Temporal Gyrus	Right	32	3.06	44, -58, 6
		Cerebellar Declive	Left	3887	4.08	-28 -70 -12

Table 9

List of White Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Children who Recovered from Stuttering (R) and Children with Persistent Stuttering (PS) on a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
PS>R	Cerebellar Regions	Posterior Cerebellar Declive	Right	54	3.71	46, -56, -20
		Posterior Cerebellar Tonsil	Left	38	3.25	-38 -38 -44
R>PS	Cortical Regions Frontal	Medial Frontal Gyrus	Right	95	4.14	14, 64, -2
		Superior Frontal Gyrus	Left	133	4.07	-20, -12, 62
		Medial Frontal Gyrus	Right	101	3.95	6, 54, 10
		Superior Frontal Gyrus	Right	58	3.32	32, 32, 52
		Inferior Frontal Gyrus	Left	57	3.31	-50, 8, 26
		Medial Frontal Gyrus	Right	31	3.20	8, 20, 46
		Medial Frontal Gyrus	Right	40	3.08	8, 38, 38
	Cortical Regions Occipital-Temporal Parietal	Cuneus	Right	394	3.78	12, -100, 8
		Inferior Occipital Gyrus	Left	126	3.42	-46, -92, -6
		Inferior Parietal Lobule	Left	36	3.22	-52, -28, 44
		Cuneus	Right	43	3.17	24, -84, 14
		Cuneus	Left	79	3.10	-24, -78, 6
		Inferior Temporal Gyrus	Right	53	3.07	60, -8, -34
		Lingual Gyrus	Left	64	3.05	-14, -64, -2
	Cerebellar Regions	Cerebellar Tonsil	Right	102	4.00	52, -56, -38
		Cerebellum	Left	199	3.33	-12 -76 -40

Table 10

List of Gray Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Children who Recovered from Stuttering (R) and Normally Fluent Children (NS) on a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
R>NS	Cortical Regions Frontal	Middle Frontal Gyrus	Right	81	3.41	42, 66, 12
	Cerebellar Regions	Cerebellar Declive	Left	41	3.25	-30 -68 -14
		Cerebellar Declive	Right	89	3.17	34, -80, -20
	Cortical Regions Occipital-Temporal	Inferior Occipital Gyrus	Left	88	3.51	-24 -90 -10
		Middle Temporal Gyrus	Left	40	3.47	-44, 6, -32
NS>R	Cortical Regions Frontal	Middle Frontal Gyrus	Left	48	3.81	-28, 22, 26
		Cingulate Gyrus	Right	34	3.47	22, -10, 38

Table 11

List of White Matter Regions, Cluster Size, Coordinates, and Peak Z-scores of Locations Found Significantly Different Between Children who Recovered from Stuttering (R) and Normally Fluent Children (NS) on a Two-Sample t-test (p< 0.005) uncorrected

		Location	Laterality	Cluster Size in Voxels	Z-Score	Talairach Coordinates (x, y, z)
R>NS	Cortical Regions Frontal	Medial Frontal Gyrus	Right	132	5.16	8, 56, 8
		Superior Frontal Gyrus	Right	296	4.69	16, 26, 66
		Middle Frontal Gyrus	Left	49	3.44	-30, 18, 48
		Orbital Gyrus	Right	84	3.37	24, 38, -28
	Cerebellar Regions	Cerebellar Tonsil	Right	117	3.74	44, -58, -40
		Cerebellar Pyramis	Right	157	3.41	28, -60, -28
	Cortical Regions Occipital-Temporal Parietal	Superior Temporal Gyrus	Right	124	4.27	20, 20, -40
		Cuneus	Right	144	3.80	16, -100, 8
		Inferior Parietal Lobule	Right	38	3.46	54, -36, 24
		Lingual Gyrus	Left	74	3.56	-24, -72, 4
		Precuneus	Right	67	3.41	2, -64, 40
NS>R	Cortical Regions Frontal	Precentral Gyrus	Right	34	4.17	40, 16, 40
	Cerebellar Regions	Posterior Cerebellar Uvula	Left	79	3.57	-10 -94 -24
		Posterior Cerebellar Tuber	Right	70	3.37	52, -90, -30

CHAPTER VII: FIGURES

Figures 1-10

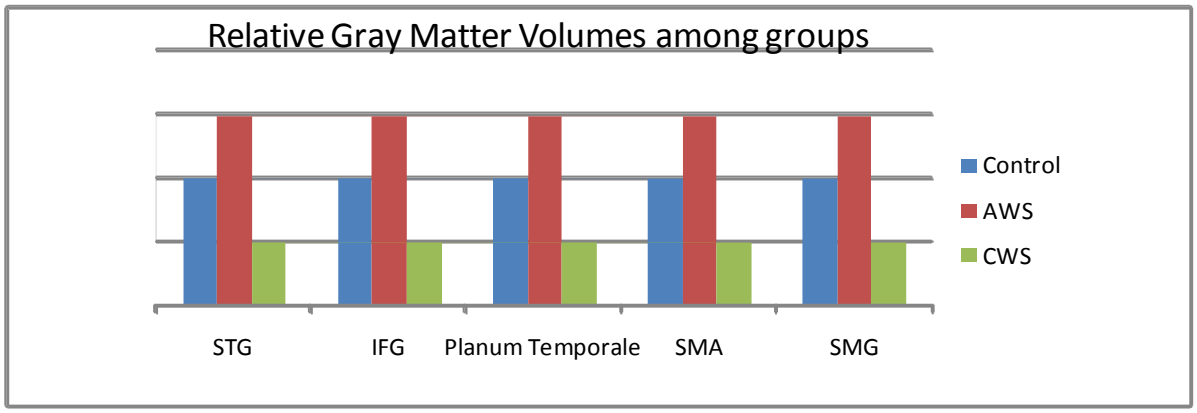

Figure 1: A *schematic* of gray matter volume differences among children who stutter (CWS), adults who stutter (AWS), and normally fluent control groups (Control) as reported in the literature. Overall, previous structural studies reported that children who stutter had less gray matter volumes than normally fluent children, while adults who stutter had increased gray matter volume compared to normally fluent adult controls in superior temporal gyrus (STG), inferior frontal gyrus (IFG), planum temporale, supplementary motor area (SMA), and supramarginal gyrus (SMG).

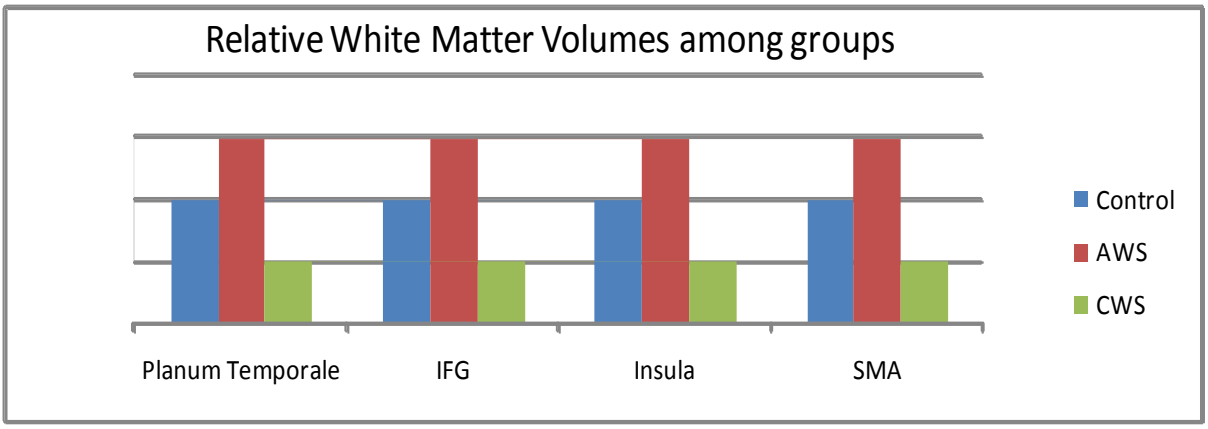

Figure 2: A *schematic* of white matter volume differences among children who stutter (CWS), adults who stutter (AWS), and normally fluent control groups (Control) as reported in the literature. Based on the previous reports of structural studies, children who stutter had less white matter volume than normally fluent children, while adults who stutter had more gray matter volume than normally fluent adult controls in planum temporale, inferior frontal gyrus (IFG), insula, and supplementary motor area (SMA).

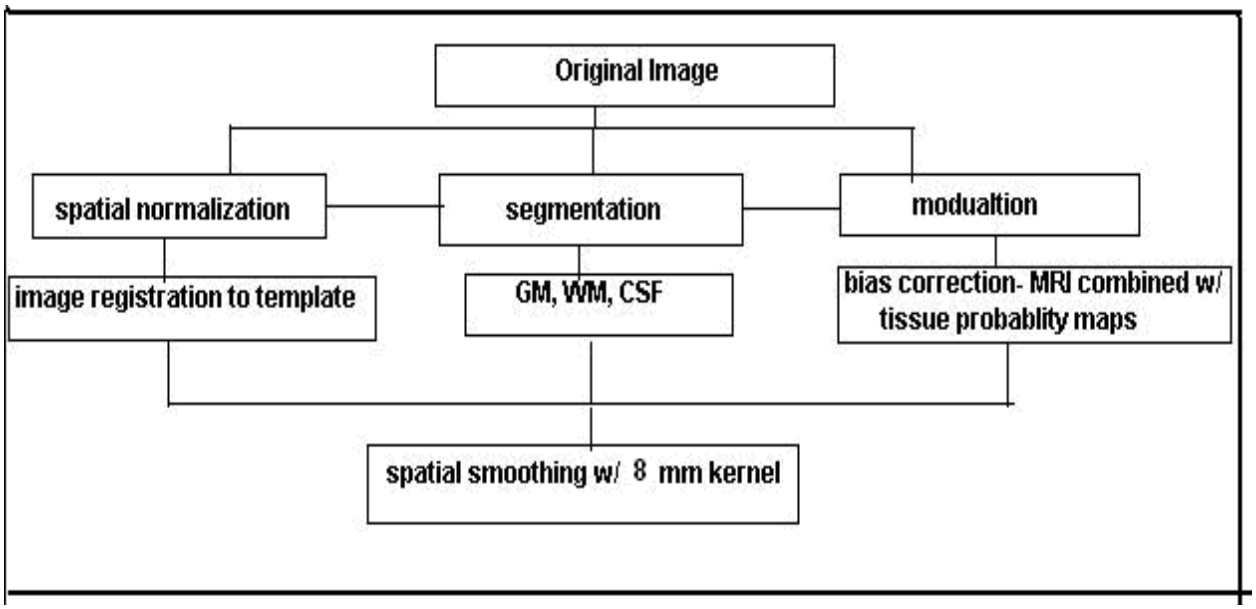

Figure 3: Processing steps involved in voxel-based morphometric analyses used in this study. All processing steps were carried out using the default options in SPM5. Segmentation step produces three different tissue classes: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Detailed description is available in SPM5 manual (http://www.fil.ion.ucl.ac.uk/spm/).

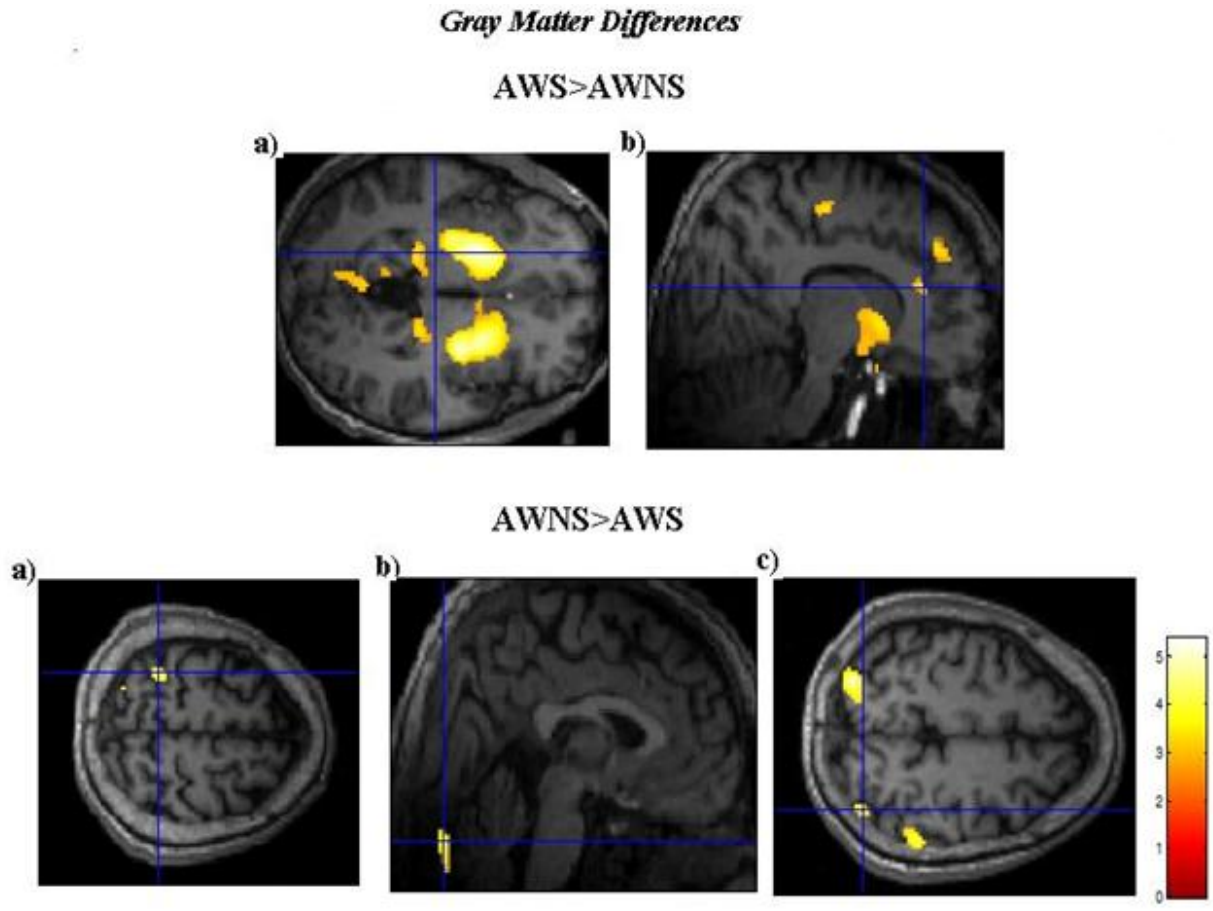

Figure 4: Gray matter volume differences between adults who stutter (AWS) and normally fluent controls (AWNS). AWS>AWNS: a) Axial view of bilateral putamen, bilateral basal ganglia, and left posterior cingulate. b) Sagittal view of right anterior cingulate gyrus, thalamus, superior frontal gyrus, parietal lobule subgyral AWNS>AWS : a) Top view of left postcentral gyrus, b) sagittal view of left cerebellum, c) axial view of bilateral precuneus and right superior parietal lobule

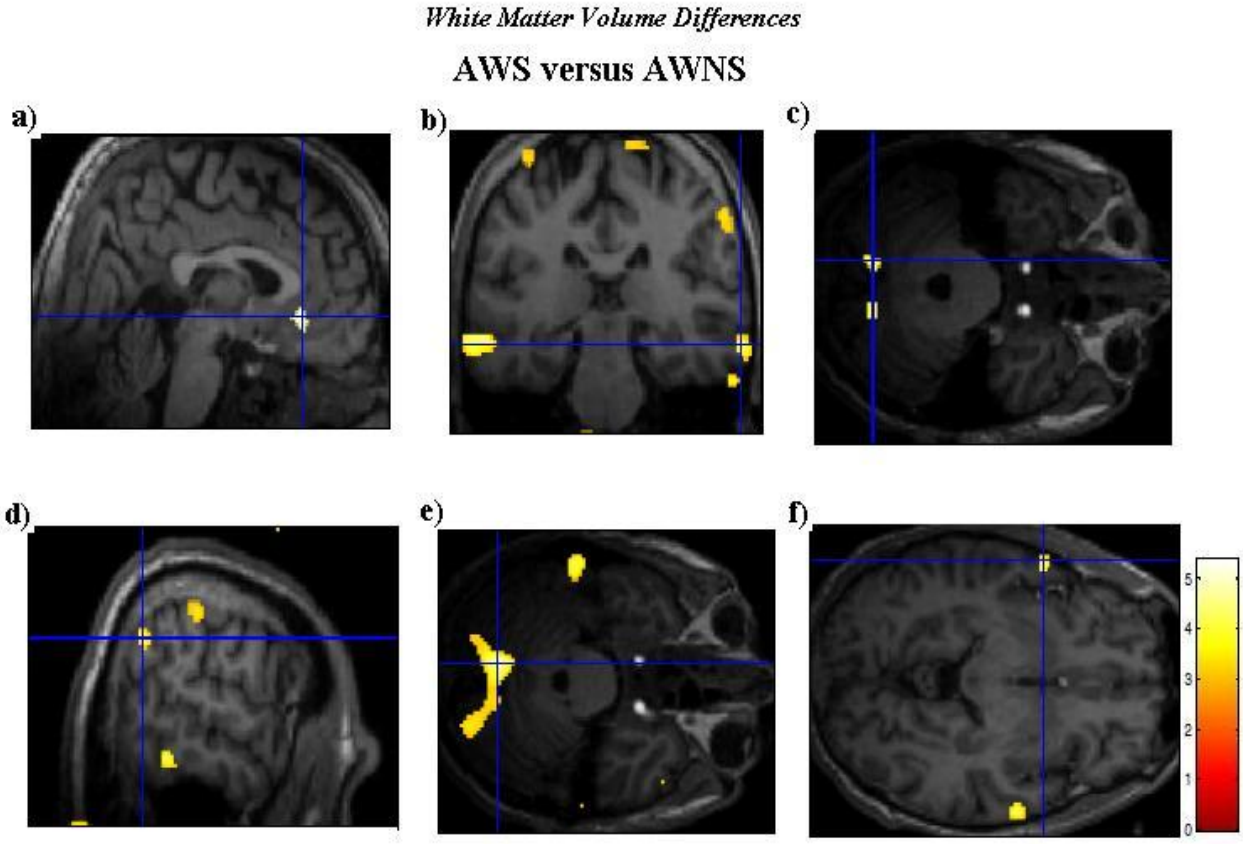

Figure 5: White matter volume differences between adults who stutter (AWS) and normally fluent controls (AWNS). AWS> AWNS: a) Sagittal view of left anterior cingulate gyrus. AWNS> AWS: b) Coronal view of bilateral middle temporal gyri, right precentral gyrus, left precentral gyrus c) Axial view of bilateral cerebellar tonsil d) Sagittal view of right supramarginal gyrus, right postcentral gyrus e) Axial view of posterior cerebelllar pyramis, left parahippocampal gyrus f) Axial view of left and right superior temporal gyri

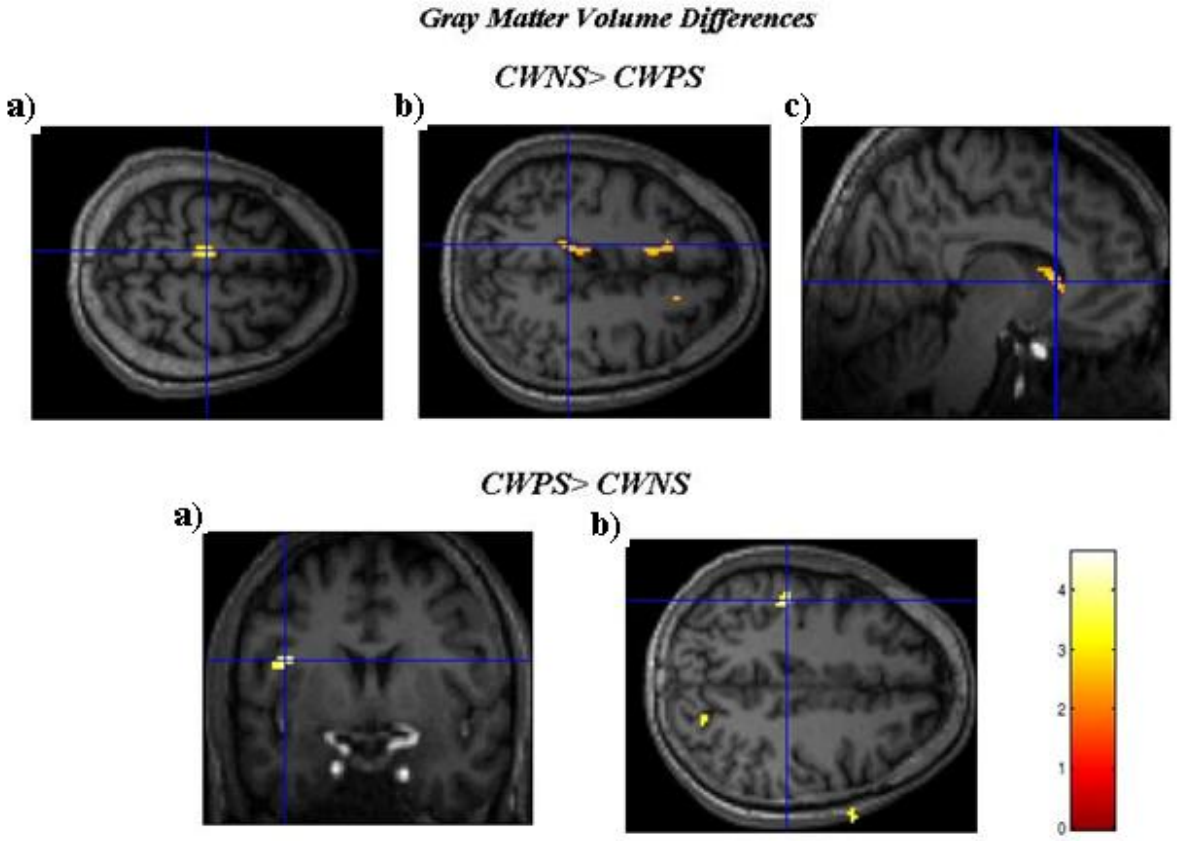

Figure 6: Gray matter volume differences between children with persistent stuttering (CWPS) and normally fluent children (CWNS). CWNS>CWPS: a) Top view of left precentral gyrus b) Axial view of left paracentral gyrus, and left medial frontal gyrus c) Sagittal view of left caudate nucleus. CWPS>CWNS: a) Coronal view of left inferior frontal gyrus b) Axial view of left post central gyrus and right precuneus

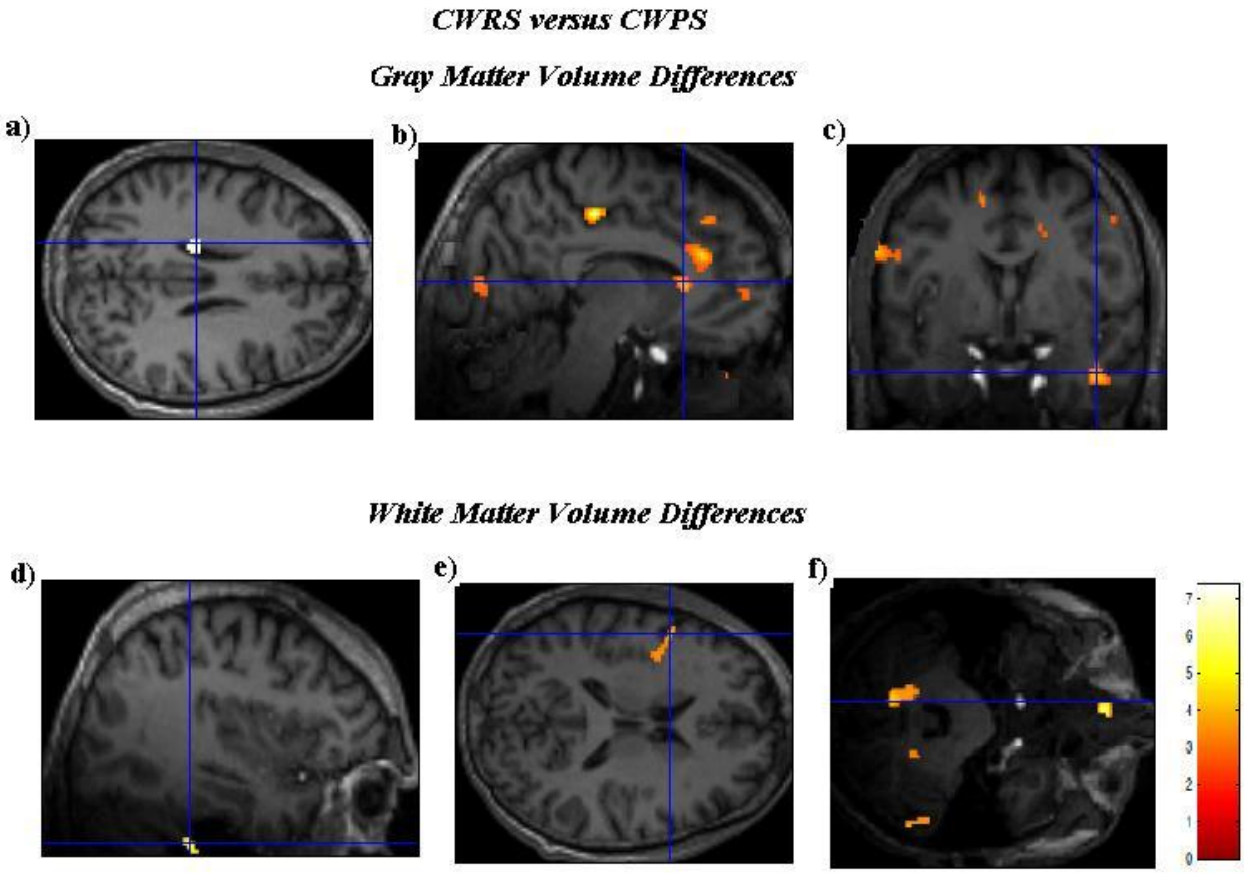

Figure 7: Gray and white matter volume differences between recovered children (CWRS) and persistent stuttering children (CWPS) groups. Gray matter (GM) Volume: a) Persistent>Recovered- Axial view of increased gray matter volume in left cingulate gyrus b) Recovered> Persistent- Sagittal view of left anterior cingulate, superior frontal gyrus c) Recovered>Persistent- Coronal view of right middle temporal gyrus, left superior and middle frontal gyri. White matter (WM) Volume: d) Persistent> Recovered- Sagittal view of left posterior cerebellar tonsil e) Recovered>Persistent- Axial view of left inferior frontal gyrus f) Recovered> Persistent- Axial view of left cerebellum and right posterior cerebellar tonsil.

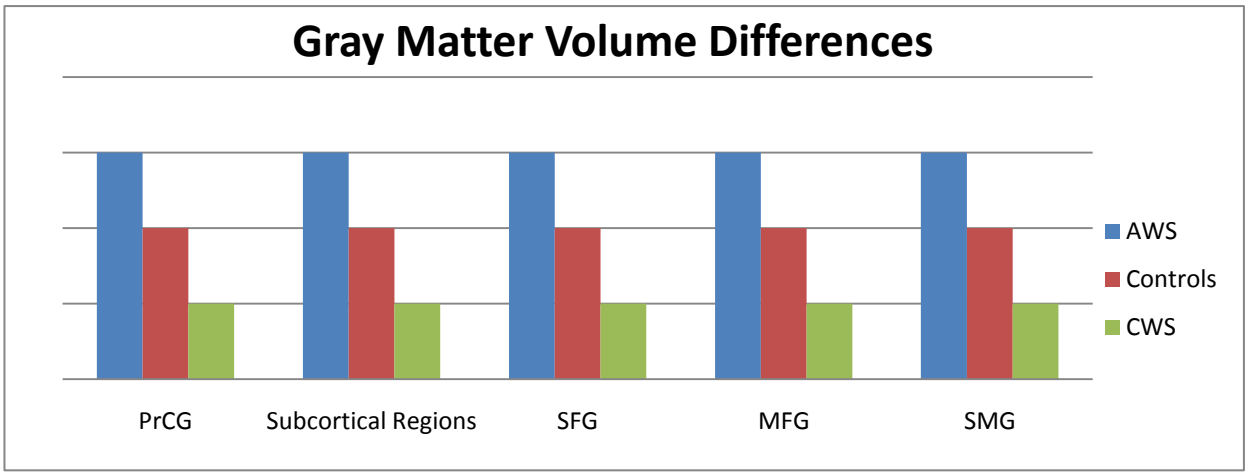

Figure 8: A *schematic* of gray matter volume differences among children who stutter (CWS), adults who stutter (AWS), and normally fluent control groups (for simplicity control speakers are not separated into age groups). Overall, the results of the current study showed that children who stutter had less gray matter volumes than normally fluent children, while adults who stutter had increased gray matter volume compared to normally fluent adult controls in precentral gyrus (PrCG), subcortical regions such as putamen and thalamus in adults and caudate nucleus in children; superior frontal gyrus (SFG), middle frontal gyrus (MFG), and supramarginal gyrus (SMG).

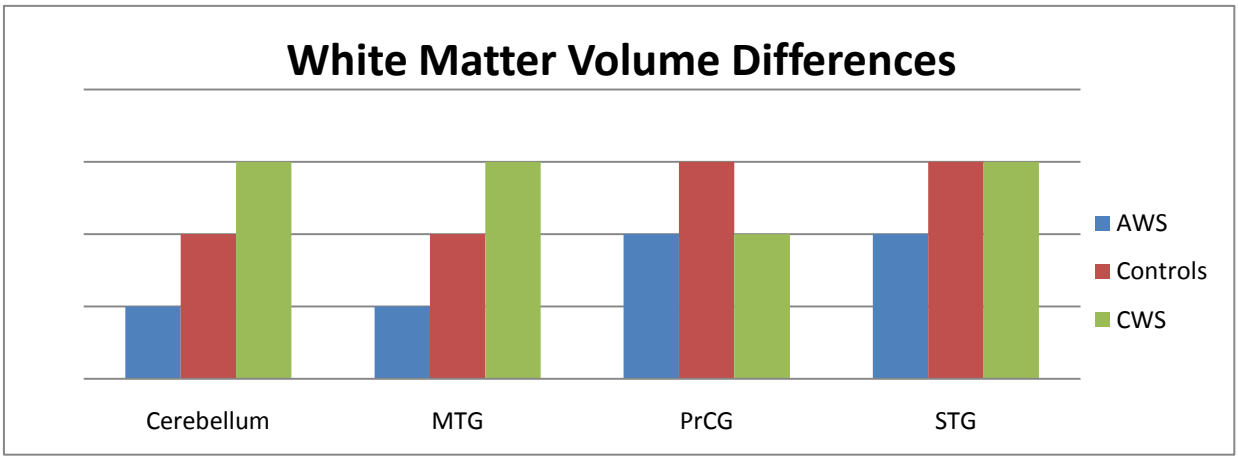

Figure 9: A *schematic* of gray matter volume differences among children who stutter (CWS), adults who stutter (AWS), and normally fluent control groups (for simplicity control speakers are not separated into age groups). Overall, the results of the current study showed that adults who stutter had reduced white matter volume in cerebellum, middle temporal gyrus (MTG), precentral gyrus (PrCG), and superior temporal gyrus (STG) compared to normally fluent adult controls. CWS showed more white matter than normally fluent children controls in cerebellum, and MTG. CWS showed less white matter in PrCG, but no difference in white matter volume in STG compared to controls.

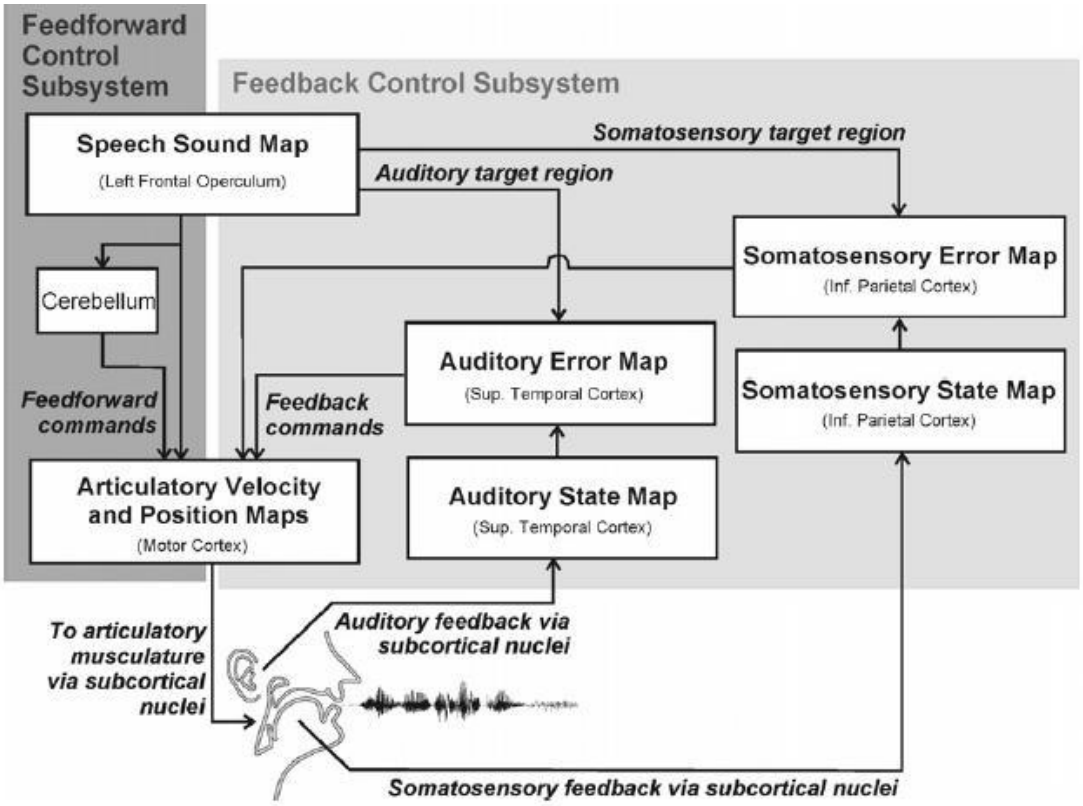

Figure taken from Guenther (2006). Schematic of the DIVA model. Projections to and from the cerebellum are simplified for clarity.

Figure 10: Schematic of the DIVA (Directions into Velocities of Articulators) model of speech production.

BIBLIOGRAPHY

Abell, F., Krams, M., Ashburner, J., Passingham, R. E., Friston, K. J., Frackowiak, R. S. J., Happe, F., Frith, C. D., and Frith, U. (1999). The neuroanatomy of autism: A voxel based whole brain analysis of structural scans. *NeuroReport, 10,* 1647–1651.

Ackermann, H. (2008). Cerebellar contributions to speech production and speech perception: psycholinguistic and neurobiological perspectives. *Trends in Neurosciences, 31 (6),* 265-272.

Alm, P.A. (2004). Stuttering and the basal ganglia circuits: a critical review of possible relations. *Journal of Communication Disorders, 37,* 325–369.

Ambrose, N.G., Yairi, E., & Cox, N. (1993). Genetic aspects of early childhood stuttering. *Journal of Speech and Hearing Research, 36,* 701-706.

Ambrose, N.G., Cox, N.J. & Yairi, E. (1997). The genetic basis of persistence and recovery in stuttering. *Journal of Speech, Language, and Hearing Research, 40,* 567-580.

Ambrose, N.G., Yairi, E. (1999). Normative Disfluency Data for Early Childhood Stuttering. *Journal of Speech, Language, and Hearing Research, 42,* 895-909.

Andrews, G., Morris-Yates, A., Howie, P., and Martin, N. (1991). Genetic factors in stuttering confirmed. *Arch. Gen. Psychiatry, 48,* 1034–1035.

Ashburner, J., Friston, K.J., (2000). Voxel-based morphometry- The methods. *NeuroImage, 11,* 805–821.

Ashburner, J., Friston, K. J. (2001). Why voxel-based morphometry should be used. *NeuroImage, 14(6),* 1238-1243.

Ashburner, J., Friston, K. J. (2005). Unified segmentation. *NeuroImage, 26,* 839-851.

Assaf, Y. & Pasternak, O. (2008). Diffusion tensor imaging (DTI)- based white matter mapping in brain research: A review. *Journal of Molecular Neuroscience, 34,* 51–61.

Beal, D. S., Gracco, V. L., Lafaille, S. J., De Nil, L. F. (2007) Voxel-based morphometry of auditory and speech-related cortex in stutterers. *Neuroreport, 18,* 1257–1260.

Bloodstein, O. & Bernstein Ratner, N. (2008). *A handbook on stuttering. (6th ed).* Thomson-Delmar.

Braun, A.R., Varga, M., Stager, S., Schulz, G., Selbie, S., Maisog, J.M., Carson, R.E., Ludlow, C.L. (1997). Altered patterns of cerebral activity during speech and language production in developmental stuttering: An H215O positron emission tomography study. *Brain, 120,* 761–784.

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., Fox, P.T. (2005). Stuttered and fluent speech production: An ALE meta-analysis of functional neuroimaging studies. *Human Brain Mapping, 25,* 105–117.

Burgund, D.E., Hyunseon, C.K., Kelly, J.E., Buckner, R.L., Snyder, A.Z., Petersen, S.E., Schlaggar, B.L. (2002). The feasibility of a common stereotactic space for children and adults in fMRI studies of development. *Neuroimage, 17,* 184-200.

Burton, E.J., McKeith, I.G., Burn, D.J., Williams, E.D., O'Brien, J.T. (2004) Cerebral atrophy in Parkinson's disease with and without dementia: A comparison with Alzheimer's disease, dementia with Lewy bodies and controls. *Brain, 127,* 791-800.

Celsis, P., Boulanouar, K., Ranjeva, J.P., Berry, I., Nespoulous, J.L., and Chollet, F. (1999). Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. *NeuroImage, 9,* 135-144.

Chang, S. E., Erickson, K. I., Ambrose, N. G., Hasegawa-Johnson, M. A., Ludlow, C. L. (2008). Brain anatomy differences in childhood stuttering. *NeuroImage, 39,* 1333–1344.

Chang, S. E., Kenney, M. K., Loucks, T. M. J. & Ludlow, C. L. (2009). Brain activation abnormalities during speech and non-speech in stuttering speakers. *Neuroimage, 46(1),* 201-212.

Ciabarra, A. M., Elkind, M. S., Roberts, J. K. & Marshall, R. S. (2000). Subcortical infarction resulting in acquired stuttering. *Journal of Neurology, Neurosurgery and Psychiatry, 69,* 546–549.

Civier, O. (2010) *Computational Modeling Of The Neural Substrates Of Stuttering And Induced Fluency.* Boston University Thesis. Boston, MA: Boston University.

Civier, O., Tasko, S. M., and Guenther, F. H. (2010). Overreliance on auditory feedback may lead to sound/syllable repetitions: Simulations of stuttering and fluency-inducing conditions with a neural model of speech production. *Journal of Fluency Disorders, 35,* 246–279.

Craig, A., Hancock. K., Tran, Y., Craig, M. & Peters, K. (2002). Epidemiology of stuttering in the communication across the entire life span. *Journal of Speech Language Hearing Research, 45,* 1097-1105.

Craig, M. C., Zaman, S. H., Daly, E. M., Cutter, W.J., Robertson, D.M. et al. (2007). Women with autistic-spectrum disorder: Magnetic resonance imaging study of brain anatomy. *Br. J. Psychiatry, 191,* 224–228.

Curry, F. K. W., Gregory, H. (1969). The performance of stutterers on dichotic listening tasks thought to reflect cerebral dominance. *Journal of Speech and Hearing Research, 12,* 73-82.

Cykowski, M. D., Kochunov, P. V., Ingham, R. J., Ingham, J. C., Mangin, J. F., et al. (2008). Perisylvian sulcal morphology and cerebral asymmetry patterns in adults who stutter. *Cereb Cortex, 18(3),* 571-83.

Damasio, H., and Damasio, A.R. (1980). The anatomical basis of conduction aphasia. *Brain, 103,* 337-350.

De Nil, L.F., Kroll, R.M., Kapur, S., Houle, S., (2000). A Positron Emission Tomography Study of Silent and Oral Single Word Reading in Stuttering and Nonstuttering Adult. *Journal of Speech, Language, and Hearing Research, 43,* 1038-1053.

De Nil, L.F., Kroll, R.M., Lafaille, S.J.., Houle, S., (2003). A positron emission tomography study of short- and long-term treatment effects on functional brain activation in adults who stutter. *Journal of Fluency Disorders, 28,* 357-380.

Di, X., Chan, R. C., Gong, Q. Y. (2009). White matter reduction in patients with schizophrenia as revealed by voxel-based morphometry: An activation likelihood estimation meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33,* 1390–1394.

Dronkers, N.F. (1996). A new brain region for coordinating speech articulation, *Nature, 384 (6605),* 159–161.

Dunn, L. (1959). *Peabody Picture Vocabulary Test.* American Guidance Service, Circle Pines, MN.

Dworzynski K, Remington A, Rijsdijk F, Howell P, Plomin R. (2007). Genetic etiology in cases of recovered and persistent stuttering in an unselected, longitudinal sample of young twins. *American Journal of Speech Language Pathology, 16,* 169-78.

Fabbro, .F, Clarici, A., Bava, A. (1996). Effects of left basal ganglia lesions on language production. *Percept Mot Skills, 82(3),* 1291-1298.

Felsenfeld, S., Kirk, K.M., Zhu, G., Statham, D.J., Neale, M.C. & Martin, N.G. (2000). A study of the genetic and environmental etiology of stuttering in a selected twin sample. *Behavioral Genetics, 30,* 359-366.

Foundas, A. L., Bollich, A. B., Corey, D. M., Hurley, M., Heilman, K. M. (2001). Anomalous Anatomy in Adults with Persistent Developmental Stuttering: A Volumetric MRI Study of Cortical Speech-Language Areas. *Neurology, 57,* 207-215.

Foundas, A. L., Corey, D. M., Angeles, V., Bollich, A. M., Crabtree-Hartman, E., Heilman, K. M. (2003). Atypical cerebral laterality in adults with persistent developmental stuttering. *Neurology, 61,* 1378-1385.

Fox, P.T., Ingham, R., Ingham, J.C., Hirsch, T.B., Downs, J.H., Martin, C. et al. (1996). A PET study of the neural systems of stuttering. *Nature, 382,* 158-162.

Fox, P.T., Ingham, R.J., Ingham, J.C., Zamarripa, F., Xiong, J.-H., and Lancaster, J.L. (2000). Brain correlates of stuttering and syllable production: A PET performance-correlation analysis. *Brain, 123,* 1985-2004.

Franco, E., Casado, J. L., Lopez Dominguez, J. M., Diaz Espejo, C., Blanco, A. & Robledo, A. (2000). Stuttering as the only manifestation of a cerebral infarct. *Neurologia, 15(9),* 414–416.

Gaser, C., Schlaug, G. (2003). Brain Structures Differ between Musicians and Non-Musicians. *The Journal of Neuroscience, 8 (27),* 9240-9245.

Gilmore, J.H., Schmitt, J.E., Knickmeyer, R.C., Smith, J.K., Lin, W., Styner, M., Neale, M.C. (2010). Genetic and environmental contributions to neonatal brain structure: A twin study. *Human Brain Mapping, 31(8),* 1174-1182.

Giraud, A.L., Neumann, K., Bachoud-Levi, A.C., von Gudenberg, A.W., Euler, H.A., Lanfermann, H., Preibisch, C. (2008). Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering. *Brain Lang. 104*, 190--199.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N.A., Friston, K.J., and Frackowiak, R.S.J. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage, 14,* 21-36.

Gorno-Tempini, M. L., Ogar, J. M., Brambati, S. M., Wang, P., Jeong, J. H., Rankin, K. P., et al. (2006). Anatomical correlates of early mutism in progressive nonfluent aphasia. *Neurology, 67,* 1849-1851.

Guenther, F. H. (2001). Neural Modeling of Speech Production. *Proceedings of the 4th International Nijmegen Speech Motor Conference*, Nijmegen, The Netherlands, June 13-16.

Guenther, F. H. (2006). Cortical interactions underlying the production of speech sounds. *Journal of Communication Disorders, 39,* 350–365.

Guenther, F.H., Ghosh, S.S., and Tourville, J.A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and Language, 96,* 280-301.

Howell, P. (2004). Assessment of some contemporary theories of stuttering that apply to spontaneous speech. *Contemporary Issues in Communicative Sciences and Disorders, 31,* 122-139.

Howell, P. (2010) Behavioral effects arising from the neural substrates for atypical planning and execution of word production in stuttering. *Experimental Neurology, 225 (1),* 55-59.

Hulshoff Pol, H.E., Schnack, H.G., Posthuma, D., Mandl, R.C., Baare, W.F., van Oel, C., et al. (2006). Genetic contributions to human brain morphology and intelligence. *Journal of Neuroscience, 4(26),* 10235-10242.

Ilg, R., Wohlschlager, A.M., Gaser, C., Liebau, Y., Dauner, R., Woller, A., Zimmer, C., Zihl, J., Muhlau, M. (2008). Gray Matter Increase Induced by Practice Correlates with Task-Specific Activation: A Combined Functional and Morphometric Magnetic Resonance Imaging Study. *Journal of Neuroscience, 28(16),* 4210-4215.

Ingham, R.J., Fox, P.T., Ingham, J.C. & Zamarripa, F. (2000). Is overt speech a prerequisite for the neural activations associated with chronic developmental stuttering? *Brain and Language, 75,* 163-194.

Jäncke, L., Hanggi, J., Steinmetz, H. (2004). Morphological brain differences between adult stutterers and non-stutterers. *BMC Neurol., 4,* 23.

Janssen, P., Kloth, S.A.M., Kraaimaat, F.W. & Brutten, G.J. (1996) Genetic factors in stuttering: a replication of Ambrose, Yiari, and Cox's (1993) study with adult probands. *Journal of Fluency Disorders, 21 (2),* 105-108.

Kang, H.C., Burgund, E.D., Lugar, H.M., Petersen, S.E., Schlaggar, B.L. (2003). Comparison of functional activation foci in children and adults using a common stereotactic space. *Neuroimage, 19,* 16-28.

Kell, C.A., Neumann, K., von Kriegstein, K., Posenenske, C., von Gudenberg, A.W., Euler, H., Giraud, A.L. (2009). How the brain repairs stuttering. *Brain, 132(10),* 2747--2760.

Kubicki, M., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Kasai, K., Kikinis, R., et al. (2002). Voxel-based morphometric analysis of gray matter in first episode schizophrenia. *Neuroimage, 17,* 1711–1719.

Lu, C., Peng, D., Chen, C., Ning, N., Ding, G., Li, K., Yang, Y., Lin, C. (2010). Altered effective connectivity and anomalous anatomy in the basal ganglia-thalamocortical circuit of stuttering speakers. *Cortex, 46,* 49-67.

Ludlow, C.L., Loucks, T. (2003). Stuttering: a dynamic motor control disorder. *Journal of Fluency Disorders, 28,* 273–295.

Mane, A., Falcon, C., Mateos, J.J., Fernandez-Egea, E., Horga, G., et al. (2009). Progressive gray matter changes in first episode schizophrenia: a 4-year longitudinal magnetic resonance study using VBM. *Schizophrenia Research, 114(1-3),* 136-143.

Manning, W. (2009). *Clinical decision making in the diagnosis and treatment of fluency disorders. (3rd ed).* Clifton Park, NY: Thomson Learning.

Mansson, H. (2000). Childhood stuttering: Incidence and development. *Journal of Fluency Disorders, 25,* 47-57.

Max, L., Guenther, F. H., Gracco, V. L., Ghosh, S. S. & Wallace, M. E. (2004). Unstable or insufficiently activated internal models and feedbackbiased motor control as sources of dysfluency: A theoretical model of stuttering. *Contemporary Issues in Communication Science and Disorders, 31,* 105–122.

Middleton, F.A., Strick, P.L. (2001). Cerebellar Projections to the Prefrontal Cortex of the Primate. *The Journal of Neuroscience, 21(2),* 700-712.

Mulligan, H., Anderson, T., Jones, R., Williams, M. & Donaldson, I. (2001). Dysfluency and involuntary movements: A new look at developmental stuttering. *International Journal of Neuroscience, 109,* 23-46.

Muzik, O., Chugani, D.C., Juhasz, C., Shen, C., Chugani, H.T. (2000). Statistical parametric mapping: assessment of application in children. *Neuroimage, 12,* 538-549.

Newcomer, P.L., Hammill, D.D. (1992). *The Test of Language Development*. Empiric Press, Austin, TX.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9,* 97-11.

Packman, A., & Attanasio, J.S. (2004). *Theoretical issues in stuttering.* New York: Psychology Press.

Peper, J.S., Brouwer, R.M., Boomsma, D.I., Kahn, R.S., Hulsoff Pol, H.E. (2007). Genetic influences on human brain structure: a review of brain imaging studies in twins. *Human Brain Mapping, 28(6),* 464-473.

Pickett, E. R., Kuniholm, E., Protopapas, A., Friedman, J., Lieberman, P. (1998) Selective speech motor, syntax and cognitive defcits associated with bilateral damage to the putamen and the head of the caudate nucleus: A case study. *Neuropsychologia, 36,* 173-188.

Preibisch, C., Neumann, K., Raab, P., Euler, H. A., W von Gudenberg, A., Lanfermann, H., Giraud, A-L. (2003). Evidence for compensation for stuttering by the right frontal operculum. *NeuroImage, 20 (2),* 1356-1364.

Preibisch, C., Raab, P., Neumann, K., Euler, H. A., von Gudenberg, A. W., Gall, V., et al. (2003). Event-related fMRI for the suppression of speech-associated artifacts in stuttering. *Neuroimage, 19(3),* 1076-1084.

Pulvermuller, F., Huss, M., Kherif, F., Moscoso del Prado, F., Hauk, O., and Shtyrov, Y. (2006) Motor cortex maps articulatory features of speech sounds. *Proceedings of the National Academy of Sciences USA 103,* 7865-7870.

Riaz, N., Steinberg, S., Ahmad, J., Pluzhnikov, A., Riazuddin, S. & Cox, N.J., et al. (2005). Genomewide significant linkage to stuttering on chromosome 12. *American Journal of Human Genetics, 76,* 647-651.

Salmond, C. H., Ashburner, J., Vargha-Khadem, F., Connelly, A., Gadian, D. G., Friston, K. J. (2002). Distributional assumptions in voxel-based morphometry. *Neuroimage, 17,* 1027–1030.

Schlaggar, B.L., Brown, T.T., Lugar, H.M., Visscher, K.M., Miezin, F.M., Petersen, S.E. (2002). Functional neuroanatomical differences between adults and school-age children in the processing of single words. *Science, 296,* 1476-1479.

Shugart, Y.Y., Mundorff, J., Kilshaw, J., Doheny K., Doan, B., Wanyee, J., et al. (2004). Results of a genome-wide linkage scan for stuttering. *American Journal of Medical Genetics A, 124,* 133-5.

Sommer, M., Koch, M.A., Paulus, W., Weiller, C., Buchel, C., (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet, 360,* 380–383.

Soroker, N., Bar-Israel, Y., Schechter, I., Solzi, P. (1990). Stuttering as a manifestation of right-hemispheric subcortical stroke, *Eur. Neurol. 30,* 268–270.

Stager, S. V., Jeffries, K. J. & Braun, A. R. (2003). Common features of fluency-evoking conditions studied in stuttering subjects and controls: An h215o pet study. *Journal of Fluency Disorders, 28(4),* 319-336.

Steinbrink, C., Vogt, K., Kastrup, A., Muller, H. P., Juengling, F. D., KAssubek, J., et al. (2008). The contribution of white and gray matter differences to developmental dyslexia: Insights from DTI and VBM at 3.0 T. *Neuropsychologia, 46(13),* 3170-3178.

Suresh, R., Ambrose, N.G., Roe, C., Pluzhnikov, A., Wittke-Thompson, J., et al. (2006). New Complexities in the Genetics of Stuttering: Significant Sex-Specific Linkage Signals. *The American Journal of Human Genetics, 55,* 554-563.

Thomann, P.A., Toro, P., Santos, V.D., Essig, M., Schroder, J. (2008). Clock drawing performance and brain morphology in mild cognitive impairment and Alzheimer's disease. *Brain and Cognition, 67(1),* 88-93.

Thompson, P.M., Cannon, T.D., Narr, K.L., van Erp, T., Poutanen ,V.P., Huttunen, M., Lönnqvist, J., et al. (2001). Genetic influences on brain structure. *Nature Neuroscience, 4(12),* 1253-1258.

Van Borsel, J., Van Lierde, K., Van Cauwenberge, P., Guldemont, Ineke, Van Orshoven, M. (1998) Severe acquired stuttering following injury of the left supplementary motor region: A case report. *Journal of Fluency Disorders, 23,* 49–58.

Van Borsel, J., Van der Made, S. & Santens, P. (2003). Thalamic stuttering: a distinct clinical entity? *Brain and Language 85(2),* 185-9.

Viswanath, N. S., Hee, S. L. & Chakraborty, R. (2004). Evidence for a Major Gene Influence on Persistent Developmental Stuttering. *Human Biology, 76 (3),* 401-412.

Watkins, K.E., Paus, T., Lerch, J.P., Zijdenbos, A., Collins, D.L., Neelin, P., Taylor, J., Worsley, K.J., Evans, A.C. (2001). Structural asymmetries in the human brain: A voxel-based statistical analysis of 142 MRI scans. *Cerebral Cortex, 11,* 868-877.

Watkins, K. E, Vargha-Khadem, F., Ashburner, J., Passingham, R. E., Connelly, A., et al. (2002) MRI analysis of an inherited speech and language disorder: structural brain abnormalities. *Brain, 125,* 465-78.

Watkins, K.E., Smith, S.M., Davis, S., Howell, P. (2008). Structural and functionalabnormalities of the motor system in developmental stuttering. *Brain, 131,* 50–59.

Williams, K.T. (1999). *Expressive Vocabulary Test.* American Guidance Service, Inc., Circle Pines.

Wilke, M., Krageloh-Mann, I., Holland, S. K. (2007). Global and local development of gray and white matter volume in normal children and adolescents. *Exp Brain Res., 178(3),* 296-307.

Wittke-Thompson, J.K., Ambrose, N.G., Yairi, E., Roe, C., Ober, C., and Cox, N.J. (2007). Genetic studies of stuttering in a founder population. *Journal of Fluency Disorders*, 32, 33-50.

Wright, I.C., Sham, P., Murray, R.M., Weinberger, D.R., Bullmore, E.T. (2002). Genetic Contributions to regional variability in human brain structure: methods and preliminary results. *Neuroimage, 17,* 256-271.

Wu, J. C., Maguire, G., Riley, G., Fallon, J., LaCasse, L., Chin, S. et al. (1995). A positron emission tomography [18F] deoxyglucose study of developmental stuttering. *Neuroreport, 6,* 501–505.

Yairi, E. & Ambrose, N. (1992). Onset of Stuttering in Preschool Children. *Journal of Speech and Hearing Research, 35,* 782-788.

Yairi, E. & Ambrose, N. (2005). *Early childhood stuttering.* Austin: Pro-Ed, Inc.